Medical Research
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Conseil de recherches
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Towards an International
Ethic for Research with Human Beings

Pour une éthique internationale
en recherche sur les sujets humains

Documents

International Summit Conference on Bioethics
Colloque international de bioéthique

April/Avril 1987

Prepared by/Préparé par: Judith Miller

Ottawa, Canada
K1A 0W9

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Document 1

GUIDING PRINCIPLES IN BIOMEDICAL RESEARCH
PRINCIPES DIRECTEURS DE LA RECHERCHE BIOMEDICALE

Elio Sgreccia

Discussion: Gunther Patzig

Session C / Séance C

International Summit Conference on Bioethics
Colloque international de bioéthique

Principes directeurs de la recherche biomédicale

PRESENTATION: Elio Sgreccia

1. OBJET ET LIMITES DE CE RAPPORT

Le but de l'intervention de chaque rapporteur national est (si je l'ai bien compris) de présenter les principes éthiques régissant à présent l'expérimentation biomédicale.

Ceci importe toutefois du moins, à mon avis, que l'on ne se limite pas à énumérer les principes et/ou les critères généraux stricto senso éthiques, mais que l'on met également en évidence si et dans quelle mesure ceux-ci ont été codifiés aussi bien par les normes et principes juridiques internationaux et nationaux (droit italien), que par les codes internationaux d'éthique médicale, et que l'on réfléchisse finalement sur les points et les thèmes évalués de manière différente ou qui font l'objet de débats et de discussions tant dans le domaine de l'éthique que parmis les juristes.

2. LA BIOETHIQUE ET SES LIMITES

Il est bien connu que le mot "bioéthique" fut employé pour la première fois en 1971 par le biologue américain Renselaer Patter: le terme indiquait l'étude de la légitimité morale des comportements humains dans les sciences biologiques.

La première Encyclopédie de Bioéthique (l' "Encyclopedia of Bioethics" éditée à New York en 1978 par l'Institut Kennedy de la Georgetown University - Washington, D.C.) définit la bioéthique de la manière suivante: "Réflexion systématique sur les problèmes et les interventions dans le domaine biomédical à fin d'établir les limites entre ce qui est licite et ce qui ne l'est pas".

Le pourquoi de cette définition est clair, la naissance de l'éthique se situant au moment historique où les premières découvertes importantes concernant l'ADN recombinant, les manipulations génétiques et la fécondation _in vitro_ firent éclater la nécessité de discerner ce qui est moralement licite dans le domaine de ce qui est techniquement possible. Ce fut à ce moment, en effet, que les perspectives ouvertes par les progrès de la science révélèrent à l'humanité que son futur évolutif pouvait être conditionné par l'homme lui-même.

Ce but à la fois grandiose et dramatique a été atteint grâce à l'expérimentation biomédicale: il existe maintenant l'espoir de guérir des nombreuses maladies héréditaires, mais l'on craint au même temps une domination de l'homme sur l'homme et sur le futur du genre humain. Par conséquent, la nécessité d'une réglementation éthique des sciences biomédicales est accrue.

Il a été observé que, suite à ses découvertes scientifiques, l'homme est passé du "présent indicatif" au "conditionnel": la remarque est exacte. Si, jusqu'il y a quelque temps, on disait: "un enfant a été conçu"; "un enfant est né"; "il est de sexe masculin"; "il est de sexe féminin"; maintenant on dit "un enfant pourrait être conçu"; "il pourrait être de sexe masculin"; "il pourrait être de sexe féminin".

Ce passage met en évidence le fait qu'il existe quelqu'un qui détient un "pouvoir": ce pouvoir demande une éthique à la fois au niveau d'orientation comme au niveau de guarantie.

Les perspectives de la bioéthique s'étant progressivement élargies, celle-ci englobe dès quelques années aussi bien les problèmes éthiques pour ainsi dire classiques (contrôle et limitation des naissances; avortement; expérimentation clinique, euthanasie, etc.) que les problèmes les plus récents de la biologie, de la génétique et de la fécondation. Tous ces problèmes se situent à leur tour dans un contexte plus général qui concerne les questions fondamentales de l'éthique dans l'expérimentation: limites et techniques de l'expérimentation, avortement et échelonnement des naissances; transplantation d'organes et de tissus par prélèvement d'un donneur vivant ou d'un foetus; acharnement thérapeutique et euthanasie; manipulations du cerveau, psychiatriques et non.

Le troisième stade de l'évolution de la bioéthique a pris en considération les influences que l'homme peut exercer sur la vie et la santé par l'entremise des programmes politiques et économiques en matière de santé.

Alors que les individus s'attendent que "le bien-être physique, psychologique et social complet leur soit garanti par les Etats, ceux-ci sont confrontés avec le problème de limiter la dépense publique: par conséquent, le risque que les malades soient selectionnés sur la base de critères purement économiques n'est pas un risque simplement hypothétique. Les "raisons du malade" ne sont plus en équilibre avec les "raisons de l'Etat"

Entre temps, le problème énorme de l'inégalité des structures et des soins de santé dans les pays occidentaux et dans les pays du tiers monde se déroule sous nos yeux: voilà un problème éthique qui concerne à la fois les différents Etats et la communauté internationale toute entière.

Au quatrième stade de son évolution, la bioéthique est d'ores et déjà appelée à réfléchir sur les problèmes concernant l'équilibre de l'échosystème planétaire: les effets néfastes de la pollution, aussi bien que la manipulation génétique des végétaux et des animaux, demandent en effet que la bioéthique s'interroge sur les devoirs de l'homme vis-à-vis de son ambiance.

Si l'expérimentation a été jusqu'ici le point central de toute analyse bioéthique, il en sera de même dans le futur, car c'est par cette voie que la catastrophe biologique ou la mutation des formes de vie existant sur la terre pourrait se vérifier ou non.

3. BIOETHIQUE ET DROITS DE L'HOMME

Dans son chemin historique vers la détermination des comportements licites et non, la bioéthique a - pour ainsi dire - rencontré les normes et les principes juridiques internationaux concernant les droits de l'homme et les libertés fondamentales.

Rappelons à ce propos la question fondamentale évoquée au procès de Nuremberg: le pouvoir politique et militaire, peut-il dominer la vie des individus?

La réponse a été donnée par la Déclaration Universelle des droits de l'homme des Nations Unies et par toutes les Déclarations et Conventions internationales qui ont codifié le devoir de respecter les droits individuels fondamentaux, y compris - notamment et surtout - le droit à la vie et à l'intégrité physique.

L'application des droits fondamentaux est guarantie au niveau régional (notamment en Europe, mais dans quelque mesure aussi en Afrique) par des organes ad hoc, qui veillent à ce que les législations étatiques se conforment aux dispositions du droit international conventionnel.

Le processus de codification des droits de l'homme au niveau international a donné vie jusqu'à présent à une vaste série de Conventions, Résolutions, Recommandations et Chartes qui (bien que leur force contraignante vis-à-vis des Etats soit parfois assez faible) ont pourtant un contenu et une valeur éthiques.

Je me limite à mentionner à cet égard la Rec. n.934 du 26 janvier 1981 sur les manipulations génétiques et la Rec. n.1046 de septembre 1986 concernant l'expérimentation sur les foetus et les embryons, toutes les deux éditées par le Conseil de l'Europe.

Voilà un autre témoignage de l'importance de l'expérimentation biomédicale et de la réglementation législative de celle-ci de principe du respect des droits de l'homme se retrouve également dans plusieurs codes d'éthique médicale élaborés par les associations internationales des médecins et des membres du personnel de santé. Le Code de Helsinki (1964) et les principes du CIOMS visant spécifiquement à l'expérimentation biomédicale en sont une épreuve.

C'est pour cela que toute réflexion bioéthique, bien qu'essentiellement philosophique, doit se rapporter également aux instruments juridiques concernant les droits de l'homme et aux codes internationaux d'éthique médicale: la bioéthique, il est vrai, ne s'identifie pas à ces instruments, mais ceux-ci sont le reflet et l'expression de valeurs éthiques universellement acceptées.

4. BIOETHIQUE ET MORALES

Référence doit également être faite aux principes élaborés au sein des Eglises (Catholique, Anglicane, Evangéliques) et des différentes religions, y compris les communautés hébraiques.

Le problème des limites de l'expérimentation biomédicale y est en effet bien présent, surtout en ce qui concerne les foetus et les embryons: le principe fondamental est encore une fois celui de respect de la vie humaine, y compris les embryons.

5. BIOETHIQUE ET EXPERIMENTATION: PRINCIPES ET CONFLITS DE PRINCIPES

En égard aux problèmes concernant spécifiquement l'expérimentation, la bioéthique - bien qu'elle puisse se prévaloir du contenu des normes juridiques régissant les droits de l'homme, des principes de la déontologie médicale et des enseignements moraux - n'est pas encore toujours susceptible d'offrir une solution valable pour tous et partout.

A cause de la variété des éléments mis en jeu par l'expérimentation (autonomie de la science et liberté de la recherche, primauté de la science ou de la société, protection et respect de la personne, pluralité des cultures et des principes éthiques à l'intérieur des sociétés occidentales) plusieurs modèles bioéthiques ont été en effet élaborés.

a) D'après un des ces modèles, la libertè et l'autonomie de la science constitueraient les principes fondamentaux de la bioéthique.

Par conséquent, le progrès de la science, voire de l'expérimentation, devrait être secondé sans aucune ingérence externe; à savoir, il pourrait se fonder sur l'autodiscipline des chercheurs.

La science et la recherche scientifique n'étant jamais dangereuses en soi, elles ne nécessitent aucune réglementation sociale: l'éthique (intrinsèque) de la sciences peut donc se baser sur la rigueur et l'objectivité des méthodes, la collaboration légale entre chercheurs et la communication des résultats. Bref, l'autocontrôle des chercheurs est la clef de voûte de la protection de la vie et de l'intégrité physique des êtres humains (y compris les chercheurs eux-mêmes) vis-à-vis des risques de l'expérimentation.

b) Un autre modèle bioéthique (que l'on pourrait définir de pragmatique) se fonde sur l'utilité sociale de la recherche et de l'expérimentation.

L'expérimentation étant en effet le seul moyen susceptible d'améliorer la santé individuelle et collective, elle ne devrait avoir ni limites ni entraves: le critère éthique fondamental se situe au niveau de l'évaluation des risques et des bénéfices escomptés par rapport à la société toute entière, considérée comme un "sujet global".

La nécessité du consentement libre et éclairé des personnes concernées n'est pas mise en discussion; toutefois, lorsque l'expérimentation ne peut être entamée que sur des incapables ou lorsque les personnes concernées n'ont pas de discernement, le profit de la société doit l'emporter sur la liberté individuelle.

Ce principe a été déjà mis en pratique dans l'expérimentation sur les aliénés et les personnes atteintes de troubles mentaux graves, sur les mineurs et sur les embryons: du reste, les directives élaborées par le CIOMS révèlent une propension accrue vers le critère du "profit social" par rapport à la Déclaration de Helsinki.

Bref, le "but thérapeutique" n'est pas axé sur le profit direct et immédiat du sujet de l'expérimentation, mais sur le possible profit futur des tiers.

c) De nos jours, un autre modèle bioéthique est en train de se consolider: le modèle sociologique.

Puisque des valeurs culturelles différentes existent à l'intérieur des sociétés pluralistes et de la communauté internationale et ces valeurs changent rapidement, le seul espoir de trouver une base éthique commune, valable pour tous et partout, se situe au niveau des Comités d'éthique nationaux, régionaux et locaux; ce qui implique évidemment, à la fois le positivisme juridique et la relativité éthique.

Les médecins réagissent de manière diverse vis-à-vis de cette idée: les comités d'éthique sont considérés parfois comme une protection, parfois comme un escamotage de ses responsabilités.

d) Finalement (last but not least) il existe un modèle éthique qui affirme la primauté de la personne sur la liberté de la science et sur le profit social, voir que le fondement de la bioéthique réside en toute circonstance dans le respect de la dignité, de la liberté et de la responsabilité de tous et de chaque individu.

Voilà le modèle qui ressort des normes juridiques concernant les droits de l'homme et surtout des morales, d'après lesquels le respect de l'être humain doit constituer le dénominateur commun indérogable de toute confrontation et de tout dialogue culturel.

Par conséquent, l'expérimentation doit être réglée de la manière suivante: l'évaluation préalable du rapport risques - bénéfices doit être rigoureuse: aucune expérimentation ne peut être entamée lorsque les risques l'emporteraient sur les bénéfices escomptés; en ce qui concerne l'expérimentation non thérapeutique, le consentement libre et éclairé des personnes concernées doit être sollicité et obtenu, de sorte qu'aucune expérimentation à but non thérapeutique ne peut être entamée sur les aliénés, sur les mineurs, sur les incapables juridiques qui n'ont pas de discernement et sur les embryons, auxquels s'appliquent les mêmes droits fondamentaux; l'expérimentation à buts non thérapeutiques "à double insu" doit ètre interdite.

Plusieurs chercheurs s'opposent aux conclusions énoncées ci-haut: ils revendiquent, par exemple, la nécessité de l'expérimentation sur les aliénés pour déceler l'origine de la maladie d'Alzheimer, aussi bien que de l'expérimentation sans consentement préalable sur les malades atteints du SIDA et de l'expérimentation génétique sur les embryons in vitro. En ce qui concerne spécifiquement ces derniers, ils sont disposés à leur reconnaître certains droits en tant que "personnalités potentielles", mais ils nient qu'ils aient les mêmes droits des adultes.

En égard finalement au problème de la personnalité juridique de l'embryon, les Comités d'Ethique ne sont manifestement pas à mesure de le résoudre, ne fasse que parce qu'ils donnent des avis purement consultatifs, à supposer même que leur création ne soit pas entravée (comme c'est le cas en Italie).

Inutile de préciser que, personnellement, je partage le schéma d), auquel se rallient du reste les projets de loi italiens en la matière.

6. BIOETHIQUE ET DROIT

La philosophie du droit nous a appris que la loi ne peut pas être la seule source de l'éthique ou de la morale, et que ni l'éthique ni la morale ne peuvent être codifiés in toto par les lois civiles et/ou pénales. Il est partant indispensable que l'on établisse les critères régissant le rapport entre éthique, morale et législation.

Les principes de la bioéthique reposent sur les valuers inhérentes à la personne humaine; la loi étatique, elle, vise à promouvoir le bien-être commun, à savoir le bien-être de chacun et de tous. Par conséquent, elle doit régler les relations entre les individus notamment au moyen de l'harmonisation des conflits et de la prévention des infractions.

Le rapport entre éthique, morale et législation étatique varie d'après les différentes "philosophies" du droit: les points fondamentaux à retenir me semblent toutefois être les suivants:

a) la défense de la vie humaine, qui est sans nul doute un principe éthique et moral, doit être assurée également par les lois étatiques, car l'être humain est au même temps la source et la raison de l'éthique et du droit. Par conséquent, une réglementation de l'expérimentation biomédicale doit être empruntée par les législations nationales et internationales;

b) cette réglementation devra éviter carrément toute discrimination et toute exploitation sur l'homme. Le consentement libre et éclairé des personnes concernées devra être sollicité et obtenu pour ce qui est notamment de l'expérimentation à buts non thérapeutiques; par conséquent, celle-ci devra ètre interdite sur les sujets qui n'ont pas de discernement.

c) la clause de conscience doit être prévue pour les médecins et le personnel de santé, aussi bien que le recours en justice devant les tribunaux nationaux et les instances judiciaires internationales, aux cas où la loi étatique prévoierait que les sujets les plus faibles et les plus démunis peuvent être exploités par l'expérimentation médicale.

2. TEXTES INTERNATIONAUX D'ETHIQUE MEDICALE: PRINCIPES DEONTOLOGIQUES ET JURIDIQUES

a) A côté du Code de Nuremberg, de la Déclaration d'Helsinki-Tokyo et des "guidelines" élaborés par le CIOMS, d'autres principes concernant l'éthique de la recherche biomédicale ont été arrêtés au niveau international.

Par conséquent, l'inventaire des textes essentiels de la déontologie médicale internationale doit également prendre en considération:

i) la Déclaration de Hawaii adoptée par l'Association Mondiale de Psychiatrie en 1977, qui a trait à la recherche en psychiatrie.

Le point 9 de la Déclaration prévoit en fait que "informed consent must be obtained before presenting a patient to a class, and, if possible, also when a case-history is released for scientific publication, whereby all reasonable measures must be taken to preserve the dignity and anonymity of the patient and to safeguard the personal reputation of the subject... In clinical research every subject must retain and exert all his rights as a patient. For children and other patients who cannot themselves give informed consent, this should be obtained from the legal next-of-kin. Every patient or research subject is free to withdraw for any reason at any time from any voluntary treatment and from any teaching or research program in which he or she participates. This withdrawal, as well as any refusal to enter a program, must never influence the psychiatrist's efforts to help the patient or subject". Et l'article 10 ajoute que: "The psychiatrist should stop all therapeutic, teaching or research programs contrary to the principles of this Declaration";

ii) la Réglementation en situation de conflit armé élaborée pour l'A.M.M. à la Havane (1956), modifié à Istambul (1957) et à Venise (1983): article 3: "Human experimentation in time of armed conflict is governed by the same code as in time of peace; it is strictly forbidden on all persons dprived of their liberty, especially civilians and military prisoners and the population of occupied countries";

iii) la Déclaration du Comité Exécutif de l'International Union of Psychological Science (1976), aux termes de laquelle "no psychologist, in the exercise of his or her professional functions, should accept instructions or motivations that are inspired by considerations that are foreign to the profession", de sorte qu'elle "protests solemnly against any use of scientific data or of professional methods of psychology that impair the above-mentioned rights";

iv) le Serment d'Athènes (1979) élaboré par les membres de profession de Santé exerçant dans les prisons, aux termes duquel "aucune forme d'expérimentation humaine ne peut être entreprise sur les individus incarcérés sans leur consentement formel";

v) la Déclaration de Kuweit (1981) portant le code Musuhman d'Ethique médicale. Le chapitre X qui concerne: "le médecin et les progrès biomédicaux modernes", se lit comme se suit: "there is in Islam no censorship of scientific research, be it academic ... or applied for the solution of a particular problem. Within this freedom of research, however, there shall be no subjugation of man, no harming, withholding of treatment, deceiving or otherwise exploiting him. No sin prohibited by Islam shall be committed in the name of research and physicians shall take part in the formulating and issue of religious verdicts on the lawfulness of new advances in the biomedical sciences";

vi) le Guide d'éthique médicale qui, élaboré au sein de la Conférence européenne des Ordres des Médecins à l'intention des médecins de la C.E.E., a été récemment approuvé à Paris et publié à Bruxelles (janvier 1987).

"Le progrès en médecine étant fondé sur la recherche, qui doit déboucher en définitive sur une expérimentation portant sur l'homme" (article 19), les principes fondamentaux la régissant sont fixés aux articles 20 à 22.

"Le sujet éventuel de l'expérience sera informé de manière adéquate des objectifs, méthodes et bénéfices escomptés, ainsi que des risques et désagréments potentiels, de son droit de ne pas participer à l'expérimentation et de s'en retirer à tout moment" (article 21), et "son consentement libre et éclairé, de préférence par écrit, sera recueilli" (ibidem).

"Le protocole de toute expérimentation projetée" aura été soumis au préalable à une Commission d'Ethique indépendante de l'expérimentateur pour avis et pour conseil" (article 20)

A noter que, d'après l'article 28, "les médecins doivent participer, dans la mesure de leurs compétences et des possibilités, à l'amélioration constante de la qualité des soins pour la recherche ..., de manière à offrir au patient des soins confirmes aux données de la science" et que aux termes de l'article 32 "le médecin a pour devoir de faire connaître les découvertes qu'il aura faites ou la conclusion de ses études scientifiques en matière diagnostic ou de thérapeutique. Il les soumettra à la critique de ses confrères dans les formes appropriées, avant d'en donner connaissance au public non médical". Dans cette optique, l'article 33 ajoute que "toute exploitation publicitaire d'un succès médical au profit d'une personne ou d'un groupe ou d'une école est contraire à l'éthique médicale".

Signalons finalement que "les médecins ne peuvent pas collaborer à la constitution des banques électroniques de données médicales en amoindrissant le droit du patient a l'intimité, à la sécurité et à la protection de sa vie privée" (article 9(1)). Par conséquent, "les banques de données médicales ne peuvent avoir aucun lien avec d'autres banques de donnés" (article 9(2)).

b) Instruments internationaux juridiques concernant la recherche biomédicale

L'aperçu des textes internationaux portant des dispositions en matière de recherche biomédicale doit prendre en considération une série de normes et principes juridiques dictés par les instruments qui visent à la protection des droits de l'homme et des libertés fondamentales.

i) Normes juridiques

1. Signalons tout d'abord l'article 7(1) du Pacte des Nations unies sur les droits civils et politiques (16.12.1966), aux termes duquel "nul ne sera soumis à une expérience médicale ou scientifique sans son consentement libre". La même disposition considère l'expérience scientifique sans consentement libre de la personne concernée comme une torture ou un traitement inhumain.

Le Pacte a été signé et dûment ratifié pour la plupart des Etats européens, y compris l'Italie (Loi n.881 du 25 octobre 1977).

2. Plusieurs dispositions ont été dictées pour le Comité des Ministres du Conseil de l'Europe notamment sur la base des articles 3; 5(1); 8(1); 9(1) et 10 de la Convention européenne sauvegarde des droits de l'homme et des libertés fondamentales (Rome 1951).

Rappelons à cet égard:

a) la Résolution (78) 29 du 11 mai 1978 visant à l'harmonisation des législations des Etats membres relatives aux prélèvements, greffes et transplantations des substances d'origine humaine.

Aux termes de l'article 1(1), la Résolution s'applique à tout prélèvement, greffe et transplantation et autre utilisation de substances d'origine humaine prélevées ou recueillies à des fins de thérapeutique et de diagnostic au profit de personnes autres que le donneur et aux fins de recherche. Le transfert d'embryon, le prélèvement et la transplantation de testicules et ovaires et l'utilisation des ovules et du sperme ne sont toutefois pas visées (article 1(2)).

En ce qui concerne particulièrement les prélèvements à fins de recherche, voire les prélèvements de substance provenant de personnes décédées (article 12(1)), la Résolution énonce le principe (qui n'admet pas d'exceptions) du respect de la volonté du défunt. L'article 10(1) affirme en fait que "aucun prélèvement ne doit être effectué lorsqu'il y a une opposition manifeste ou présumée du défunt, compte tenu notamment de ses convictions religieuses ou philosophiques".

Dans le cas où il n'a pas été possible de connaître la volonté du défunt, son consentement est présumé, étant donné que dans la plupart des Etats membres du Conseil de l'Europe chacun sont que des prélèvements peuvent avoir lieu et les personnes qui sont fortement opposées à un éventuel prélèvement auraient dû le faire savoir (article 10/2); "A défaut d'une volonté du défunt manifestée explicitement ou implicitement, le prélèvement peut être effectué".

"Un Etat pourra toutefois décider que le prélèvement ne doit pas avoir lieu si, après une enquête appropriée, compte tenu des circonstances visant à déterminer l'opinion de la famille du défunt et, dans le cas d'un incapable juridique survivant, celle de son représentant légal, une opposition se manifeste: lorsque le défunt était un incapable juridique, le consentement de son représentant légal peut également être exigé".

Aux termes de l'article 12(3), "la mort doit être constatée par un médecin qui n'appartient pas à l'équipe qui procédera au prélèvement, à la greffe ou à la transplantation" et l'anonymat du donneur doit être guaranti (article 13). La cession de substances ne peut être faite dans un fond lucratif (article 14).

b) la Convention du 28.1.1981, entrée en vigueur le 1.9.1982, concernant la protection des personnes à l'égard du traitement automatisé des données à caractère personnel.

Les articles 2 à 6 de la dite Convention interdisent la récolte et le classement des données à caractère personnel effectués sans le consentement libre et éclairé du sujet concerné; en toute circonstance "les données à caractère personnel révélant l'origine raciale, les opinions politiques, les convictions religieuses ou autres convictions, ainsi que les données à caractère personnel relatives à la santé ou à la vie sexuelle ne peuvent toutefois être traités à moins que le droit interne ne prévoie des garanties appropriées" (article 6).

A ce propos la Convention exige que la confidentialité des données qui concernent une personne "identifié ou identifiable" soit protégée de manière absolue et assure au même temps à tout intéressé le droit de contrôler les données qui le concernent, de veiller à ce qu'elles soient exactes, mises à jour et enregistrées de manière compatible avec les finalités de l'enregistrement et d'en obtenir la correction, le cas échéant.

c) la Résolution (73) 5 du 19 janvier 1973 portant l'Ensemble des règles minimales pour la protection des détenus. Aux termes de l'article 22, "les détenus ne peuvent être soumis à des expériences médicales ou scientifiques pouvant porter atteinte à l'intégrité de leur personne physique ou morale".

ii) Principes juridiques (voir normes juridiques dépourvues de force contraignante vis-à-vis des Etats).

a. Recommandations n.R(81)1 et n.R(83)10 du 23.1.1981 et du 23.9.1983 relatives aux banques de données médicales automatisées. Les principes fondamentaux de ces deux Recommandations sont les suivants: consentement exprès et conscient de la personne concernée après information sur l'utilisation des données recueillies; séparation (fonctionelle) des identifiants et autres données permettant l'identification de la personne des données à caractère médicales, administratives et sociales; accès aux informations limité aux membres de la profession médicale (les membres du personnel paramédical ne peuvent accéder aux informations que si et dans la mesure où cela est autorisé par la législation ou la pratique nationale) jusqu'au moment où ils cessent d'exercer leurs fonctions; utilisation et publication des informations limitées aux fins pour lesquels l'utilisateur a accès aux données enregistrées; publication en forme anonyme; sauf consentement exprès et conscient de la personne concernée, l'existence et le contenu d'un dossier médical la concernant ne peuvent être communiqués à des personnes ou organismes en dehors des domaines des soins médicaux, de la santé publique ou de la recherche médicale, à moins qu'une telle communication ne soit permise par les règles sur le secret médical.

b. Recommandation n.R(83) 2 du 22.2.1983 visant la protection juridique des personnes atteintes de troubles mentaux et placées comme patients involontaires. Puisque le placement n'est pas seulement une mesure thérapeutique mais comporte également une privation de la liberté, le traitement des aliénés doit se conformer strictement aux données de la science médicale

Par conséquent, les essais de nouveaux médicaments, aussi bien que de nouvelles techniques thérapeutiques psychiatriques sont interdits, sauf si le médecin les juge indispensables, voire s'il n'y a pas d'autre moyens de traiter le malade. En toute circonstance, il est interdit d'expérimenter de nouvelles techniques et d'administrer des traitements susceptibles de causer des dégâts permanents au cerveau ou d'altérer de manière irréversible le comportement du patient (article 5(2) et (3)), bien que le patient ait exprimé son consentement ("Un traitement qui n'est pas encore généralement reconnu par la science médicale ou qui présente un risque sérieux d'entraîner des dommages irréversibles au cerveau ou de détériorer la personnalité du patient, ne pourra être administré que si le médecin l'estime indispensable et si le patient, dûment informé, y consent expressément. Lorsque celui-ci n'est pas capable de comprendre la portée du traitement, le médecin doit soumettre la question à une autorité indépendante appropriée, désignée par la loi qui entendra le représentant légal du patient, s'il existe"; "Les essais cliniques de produits ou de techniques médicales n'ayant pas un but thérapeutique psychiatrique que sur les personnes atteintes de troubles mentaux et faisant l'objet d'une mesure de placement doivent être interdits".

Les conditions du placement sont soumises au contrôle des organes judiciaires (article 8).

c. Recommandation n.R(85) 3 du 26.3.1985 portant les devoirs juridiques des médecins vis-à-vis de leurs patients. Cette Recommandation vise en réalité (article 1, lettre a) les traitements, les interventions et les examens à but de prévention, de diagnostic, de thérapeutique ou de réadaptation, mais elle est néanmoins importante notamment en ce qui concerne la position des mineurs.

En principe, le consentement (libre et éclairé (article 5(1)), exprès et spécifique, de préférence par écrit (points 26 et 28 de l'Exposé des motifs annexé à la Rec.) alors que l'acte médical touche à l'intimité d'un patient ou présente un risque sérieux, est demandé aux parents ou aux tuteurs (article 6(1) lettre a).

Toutefois lorsque le mineur est capable de discernement, son avis est recueilli et il en est tenu compte dans toute la mesure du possible (article 6(2)). Le consentement du mineur est suffisant si la nature et le degré de gravité de l'acte médical le justifient (ibidem). Lorsque le patient est un incapable juridique pour un autre motif que l'âge mais qu'il est capable de discernement, son consentement est suffisant (article 6(3)).

d. Recommendation n.1046 (24.9.1986) de l'Assemblée Parlementaire du Conseil de l'Europe concernant l'utilisation d'embryons et foetus humains à des fins scientifiques, thérapeutiques, diganostiques, industrielles et commerciales.

Aux termes du point Aii), l'Assemblée Parlementaire recommande au Comité des Ministres d'inviter les gouvernements des Etats membres "de limiter l'utilisation industrielle des embryons et des foetus humains, ainsi que de leurs produits et tissus, à des fins strictement thérapeutiques et ne pouvant être atteints par d'autre moyens, selon les principes mentionnés dans l'Annexe, et de conformer leur droit à ceux-ci ou d'adopter des règles conformes, ces règles devant notamment préciser les conditions dans lesquelles le prélèvement et l'utilisation dans un but diagnostique ou thérapeutique peuvent être effectués".

L'Annexe précise en effet les règles qui doivent être respectées lors de l'utilisation et du prélèvement de tissus d'embryons ou de foetus humains à des fins de diagnostic ou de thérapeutique. Parmis ces règles signalons en particulier: toute intervention sur l'embryon vivant in utero ou in vitro ou sur le foetus in utero ou à l'extérieur de l'utérus à des fins diagnostiques, autres celles déjâ prévues par la législation nationale, n'est légitime que si elle a pour but le bien-être de l'enfant à naitre, et de favoriser son développement; l'utilisation de l'embryon ou du foetus mort à des fins diagnostiques est légitime; toute intervention sur l'embryon vivant in utero et in vitro ou sur le foetus vivant in utero ou à l'extérieur de l'utérus n'est légitime que si elle a pour but le bien-être de l'enfant à naître, à savoir favoriser son développement et sa naissance; la thérapeutique sur les embryons in vitro ou in utero ou sur les foetus in utero ne sera autorisée que pour les maladies des embryons présentant un diagnostic très précis, à prognostic grave ou très mauvais, sans autre solution de traitement et lorsque la thérapeutique offrira des garanties de solution raisonnables de la maladie; il est interdit de maintenir en survie artificielle les embryons ou les foetus dans le but d'obtenir des prélèvements utilisables; la thérapeutique sur les embryons et les foetus ne devra jamais avoir d'influence sur les caractères héréditaires non pathologiques, ni avoir pour but la sélection de la race; l'utilisation des embryons ou des foetus morts doit avoir un caractère exceptionnel...et respecter les règles suivants: la décision et les conditions de l'interruption de grossesse ne doivent en aucun cas être influencés par l'utilisation ultérieure possible ou souhaitée de l'embryon ou du foetus, une totale indépendance doit être garantie entre l'équipe qui procède à l'interruption de grossesse et l'équipe susceptible d'utiliser les embryons ou les foetus à des fins thérapeutiques; l'utilisation ne peut avoir lieu sans le consentement des parents ou des donneurs de gamètes, si l'identité de ces derniers est connue; l'utilisation des embryons, des foetus ou de leurs tissus ne peut être faite dans un but lucratif ou donner lieu à rémunération.

Toute création d'embryons humains par fécondation in vitro à des fins de recherche de leur vivant ou après leur mort est interdite par le point Aiii. Il en est également, d'après le point Aiv, en ce qui concerne: - la création d'êtres humains identiques par clonage ou par d'autres méthodes, à des fins de sélection de la race ou non; - l'implantation d'un embryon humain dans l'utérus d'une autre espèce ou l'opération inverse; - la fusion de gamètes humains avec ceux d'une autre espèce (le test de Hamster pour l'étude de la fertilité d'origine masculine pourrait constituer une exception, en fonction des termes stricts d'un règlement); - la création d'embryons avec du sperme d'individus différents; - la fusion d'embryons ou toute autre opération susceptible de réaliser des chimères; - l'ectogénèse; - la création d'enfants de personnes du même sexe; - le choix du sexe par manipulation génétique à des fins non thérapeutiques; - la création de jumeaux identiques; - la recherche sur des embryons humains viables; - l'expérimentation sur des embryons vivants, viable ou non; - le maintien des embryons in vitro au delà du 14e jour après la fécondation (déduction faite du temps de congélation éventuel).

Rappelons finalement que le point B de la Recommandation invite le Comité des Ministres à élaborer, en se fondant sur les points mentionnés au paragraphe 1A, une convention européenne ou tout autre instrument juridique approprié.

3. PRINCIPES ET PRATIQUES

a) Pour que les principes de la déontologie médicale énoncés au paragraphe I.2 puissent être mis en pratique, plusieurs instruments internationaux d'éthique médicale prévoient que les médecins jouissent et disposent en concret de leur liberté professionnelle et "de l'indépendance morale, technique et économique, aussi lieu dans le domaine des soins de santé, que dans le domaine de la recherche (voir point VII de la Déclaration de Venise (1983) de l'A.M.M.).

Citons à titre d'exemple le principe III de la Déclaration adoptée par la réunion plenière du Comité Permanent des Médecins de la C.E.E. lors de la séance tenue à Nuremberg le 24-25 novembre 1967 et, plus récemment, les articles 5(1) et 25 à 27 du Guide européen d'éthique médicale (l'article 5(1): "tant pour conseiller que pour agir le médecin doit disposer de son entière liberté professionnelle et des conditions techniques et morales lui permettant d'agir en toute indépendance"; l'article 25: "Pour accomplir sa mission..., le médecin a le droit à la protection légale de son indépendance professionnelle..."; l'article 26: "Le médecin agissant individuellement ou par l'intermédiaire des organisations professionnelles a pour devoir d'attirer l'attention de la collectivité sur les insuffisances dans le domaine ... l'indépendance professionnelle des practiciens"; l'article 27: "Les médecins sont tenus de participer à l'élaboration et à l'exécution de toutes les mesures collectives visant à améliorer la prévention, le diagnostic et le traitement des malades").

b) En égard aux connotations diverses que les principes énoncés dans les instruments internationaux sont susceptibles d'assumer dans les différents pays, il semble correct d'affirmer qu'au niveau régional (voire en ce qui concerne les Etats appartenant à une même région géographique) le problème se pose de manière aigue".

Les Etats membres du Conseil de l'Europe et de la C.E.E., par exemple, sont indiscutablement caractérisés par une série de concepts et de notions à la fois juridiques et éthiques communs, sur lesquels repose la mise en pratique des principes de l'éthique médicale.

Il est pourtant à souligner qu'une grande différence existe entre les législations et les codes de déontologie médicale nationaux, notamment à cause du fait que certains pays (parmi lesquels d'Italie) n'ont pas encore édicté ni des lois se conformant aux normes et principes internationaux, ni des règles d'éthique médicale se conformant aux principes éthiques affirmés au niveau international.

c) Pour ce qu'est finalement du problème des conflits entre principes fondamentaux en général et en recherche biomédicale, les normes et principes qui visent à la protection des droits de l'homme sont susceptibles de surmonter de tels conflits. Il en reste pourtant que de tels conflits peuvent se poser si et dans la mesure où un Etat n'a pas executé les normes et principes juridiques élaborés par les organismes internationaux ad hoc.

ELABORATION ET APPLICATION DES NORMES D'ETHIQUE NATIONALES

1. ELABORATION DES NORMES D'ETHIQUE NATIONALES (ITALIE)

L'Italie n'a pas encore élaboré une loi ou des règles de déontologie médicale concernant la recherche biomédicale.

L'article 2(7) de la Loi n.833 du 23 décembre 1978 prévoit en effet parmi les buts du Servizio Sanitario Nazionale (Service National de Santé) "una disciplina della sperimentazione, produzione, immissione in commercio e distribuzione dei farmaci" (la réglementation de l'expérimentation, de la production, de la vente et de la distribution des médicaments), et l'article 29(2) de la même Loi ajoute que "con legge dello Stato sono dettate norme: a) per la disciplina dell'autorizzazione alla produzione e alla immissione in commercio dei farmaci ... e per indirizzare la produzione farmaceutica alle finalità del Servizio Sanitario Nationale ...; b) per l'individuazione dei presidi autorizzati e per la definizione delle modalità della sperimentazione clinica precedente l'autorizzazione all'immissione in commercio dei farmaci" ("l'Etat promulguera les lois: a) pour réglementer l'autorisation à la production et à la vente des médicaments ... et pour conformer la production des médicaments aux buts et finalités du Servizio Sanitario Nazionale ...; b) pour déterminer les lieux autorisés et pour définir les modalités de l'expérimentation clinique qui doit précéder l'autorisation à la vente des médicaments"), mais les lois en question n'ont pas encore été promulguées.

Le droit italien en vigueur se limite par conséquent aux dispositions de l'Arrêté Royal (Regio Decreto) n.478 du 3 mars 1927, notamment à l'article 14(1), aux termes duquel "la domanda di registrazione delle specialità medicinali deve essere corredata dalla relazione sulle ricerche scientifiche eseguite, redatta da un medico" ("la demande d'enregistrement d'un médicament nouveau doit être accompagnée par un rapport concernant les expérimentations cliniques et scientifiques accomplies, rédigé et signé par un médecin"). D'après les Circolari Ministeriali (Instructions du Ministère de la Santé Publique) nn. 35 du 9 avril 1975 et n.77 du 6 septembre 1975, avant de passer à l'expérimentation humaine les effets du nouveau médicament sur les animaux, doivent être communiqués au Ministère de la Santé Publique. L'expérimentation sur l'homme n'est autorisée que si le médicament a été prouvé sans dangers sur les animaux.

Des recherches biomédicales sont toutefois accomplies par l'Instituto Superiore di Sanità (Institut Supérieur de Santé) suite aux dispositions prévues par l'article 9(3) et (4) de la Loi n.833 citée plus haut. "L'institut Publique a caractère scientifique sur la base d'un programme élaboré par le Ministère de la Santé Publique et des propositions énoncées par les Régions".

Ajoutons à ceci les articles 215 et ss. de la Loi n.644 du 2 décembre 1975, régissant les prélèvements de l'hypophyse à fins de la production de médicaments et les articles 39 à 42 de l'Arrêté du Président de la République (Decreto del Presidente della Repubblica) n.803 du 21 octobre 1975 qui permet l'emploi des cadavres (y compris les foetus) à des fins de recherche scientifique et d'enseignement.

Rappelons finalement que le don des reins entre personnes vivantes est permis depuis l'entrée en vigueur de la Loi n.458 du 26 juin 1967.

Quant au Code National de Déontologie Médicale (édicté en 1978), les articles 42 à 44 concernent l'expérimentation clinique des nouveaux médicaments et des nouvelles techniques thérapeutiques, alors que l'article 45 vise (et pourtant de manière tout-à-fait marginale) l'expérimentation non thérapeutique.

Le consentement libre, et de préférence par écrit, du malade (l'article 43(1)), aussi bien que le consentement libre et éclairé du volontaire sain ayant atteint l'âge majeur (l'article 44(2)), est requis. Les articles 43(1) et 44(1) prévoient encore l'évaluation préalable des risques et bénéfices escomptés et la publicité du protocole de l'expérimentation, portant notamment, tant sur les modalités et méthodes de la recherche, que sur les réactions de sujets, indépendamment des résultats de la recherche.

L'Italie n'a pas à présent non plus un Comité National d'Ethique chargé, entre autre, de veiller sur les protocoles de recherche et d'exprimer son avis ou son conseil à leur égard.

2. L'APPLICATION DES NORMES NATIONALES D'ETHIQUE EN RECHERCHE SUR DES SUJETS HUMAINS

De nombreux projets et propositions de loi concernant la recherche biomédicale sur les foetus et les embryons, aussi bien que le respect des droits de l'homme dans la recherche biomédicale se trouvent à présent devant le Parlement italien, mais ils sont tous manifestement dépourvus de valeur juridique.

Par conséquent, voir les considérations exprimées au point c. du paragraphe I.3.

QUESTIONS IMPORTANTES EN ETHIQUE BIOMEDICALE

1. La recherche sur des personnes dont la compétence à donner leur consentement est restreinte (enfants; détenus; aliénés; vieillards; population vulnérable).

a. Normes juridiques nationales (Italie)

L'article 32 de la Charte Constitutionnelle italienne stipule que "Nessuno puo essere obbligato a un determinato trattamento sanitario, se non per disposizione di legge. La legge non puo in nessun caso violare i limiti imposti dal rispetto della persona umana" ("Nul ne peut être astreint à un traitement sanitaire, si ce n'est que dans les cas prévus par la loi. En aucun cas la loi ne peut déroger au respect dû à la personne humaine").

Le principe du consentement, manifestement prévu pour les traitements médicaux, est affirmé également dans le domaine de la recherche biomédicale par voie d'analogie.

Toutefois, l'art 5 du Code Civil stipule que "gli atti di disposizione del proprio corpo sono vietati quando cagionino una diminuzione permanente della integrità fisica o quando siano contrari alla legge o all'ordine pubblico" ("Les actes de disposition sur son corps sont interdits lorsqu'ils produisent une diminution permanente de l'intégrité physique ou lorsqu'ils sont contraires à la loi ou à l'ordre public"). Puisque les lois en vigueur ne permettent à présent que le don du sang et des reins à fins de transplantation sur un receveur vivant, la portée de l'article 32 de la constitution en résulte par conséquent limitée.

Pour ce qui est de la recherche biomédicale licite aux termes de l'article 5 du Code Civil, le consentement du sujet en constitue le point essentiel, si bien que plusieurs dispositions du Code Pénal qualifient de délit de coups et blessures et punissent par conséquent tout comportement qui attente à l'intégrité physique de quelqu'un, si le consentement de la personne concernée n'a pas été obtenu (l'article 50 du Code Pénal). Il n'en est pas de même si le décès survient durant l'expérimentation et à cause de celle-ci, le consentement libre et éclairé du sujet n'ayant pas la valeur et les effets juridiques d'une exemption de responsabilité pénale (l'article 579 du Code Pénal).

Le manque de consentement comporte également la responsabilité civile pour dommages et intérêts (l'article 2043 et ss. du Code Civil).

En ce qui concerne plus particulièrement le consentement (voir les conditions de validité du consentent), d'après le droit italien il faut distinguer suivant l'âge et le statut juridique du sujet.

Les personnes ayant atteint l'âge majeur sont présumées capables "d'intendere e di volere" ("de comprendre et de décider") soit aux termes du Code Civil (les articles 120 et 427), soit du Code Pénal (l'article 85), sauf si elles ont été déclarées incapables juridiques par un tribunal ou s'il peut être prouvé qu'elles étaient affectées par un trouble mental dûment diagnostiqué, bien qu'elles n'étaient pas des incapables juridiques au sens strict du terme.

D'après la jurisprudence de la Cour de Cassation, en effet, la "capacità di intendere e di volere" ne peut être exclue que par l'arrêt du juge ou par la présence d'une maladie mentale au sens propre du terme (voir également les articles 88 et 89 du Code Pénal).

Par conséquent, les vieillards, les toxicomanes, les détenus et même les aliénés (malades mentaux) sont présumés en principe capables de donner leur consentement.

Pour ce qui est des incapables juridiques à cause de l'âge, la loi italienne n'établit aucune distinction entre les sujets qui sont capables de discernement et ceux qui n'en sont pas capables.

D'après l'article 30 de la Charte Constitutionnelle et de nombreuses dispositions du Code Civil, en effet, les parents ou les tuteurs sont les représentants légaux des mineurs; par conséquent, c'est à eux qu'il incombe en toute circonstance le droit de donner ou de refuser le consentement.

En ce qui concerne finalement les incapables juridiques pour un motif autre que l'âge, le consentement est demandé au représentant légal (curatore o tutore).

b. Normes nationales de déontologie médicale (Italie)

L'article 39 du Code National de déontologie médicale italien de 1978 prévoit que "Il medico non deve intraprendere alcun atto medico che comporti un rischio per il paziente senza il consenso valido del malato o delle persone da cui questo è rappresentato se minorenne o incapace, salvo lo stato di necessità e sempre che il paziente non sia in grado di dare un valido consenso" ("Le médecin ne doit accomplir aucun acte médical qui comporte un risque pour le patient sans que celui-ci ou les personnes qui le représentent s'il s'agit d'un mineur ou d'un incapable, aient exprimé leur consentement valable, exception faite pour les cas d'urgence").

Cette disposition vise en toute évidence l'accomplissement des actes médicaux; elle est pourtant appliquée à la recherche biomédicale par voie d'analogie.

c. Dispositions internationales juridiques et d'éthique médicales

Voir dispositions citées aux paragraphes I.2. lett.a, I.2. lett.b et II.1.

Il résulte de la confrontation des règles nationales avec les normes et principes internationaux que des nombreux problèmes demeurent irrésolus, notamment en ce qui concerne le consentement des parents ou tuteurs à l'égard des enfants incapables de discernement et le consentement des vieillards et des aliénés.

Pour ce qui est en particulier du problème des enfants, rappelons que la représentation légale des droits fondamentaux dans le chef des parents (ou des tuteurs) devraient être exclue.

2. RECHERCHE SUR LES EMBRYONS ET LES FOETUS

a et b. L'Italie n'a pas encore élaboré aucune norme juridique ni aucune règle d'éthique médicale concernant les foetus et les embryons.

L'article 7 de l'Arrêté du Président de la République (Decreto del Presidente della Repubblica) n.803 du 21 octobre 1975 se limite en effet à prévoir que "les produits issus de la grossesse, y compris les foetus de moins de 20 semaines, peuvent être enterrés dans les cimetières avant ou après qu'ils ont été délivrés aux universités à buts de recherche et d'enseignement" (les articles 39 et 40), et l'article 7 de la Loi n.194 du 22 mai 1978 stipule que "lorsque le foetus a la possibilité de vivre séparé du corps de la mère, l'interruption de la grossesse peut être effectuée seulement si la grossesse elle-même ou l'accouchement mettent en grave danger la vie de la femme enceinte (l'article 6 lett. a de la même Loi). Le médecin qui accomplit l'intervention doit adopter toute mesure apte à sauvegarder la vie du foetus".

Aucune disposition n'existe non plus en matière de diagnostic anténatal.

c. En ce qui concerne les principes juridiques internationaux visant la recherche sur les embryons et les foetus, voir paragraphe I.2.b.ii lettre d.

3. EXAMEN ETHIQUE DES ETUDES PILOTES ET INTRODUCTION DES NOUVELLES THERAPIES

a et b. Pas de dispositions en droit et dans la déontologie médicale italiens.

c. Voir supra, paragraphe I.2.a).

4. Recherche industrielle: questions éthiques

a, b et c. Pas de dispositions au niveau européen.

5. Normes d'éthique pour la recherche internationale et interculturelle

CONCLUSION

De façon générale, on peut constater un accord de base entre, soit les principes juridiques-déontologiques acceptés dans le camp national et international que les préceptes de l'éthique personnalistique; toutefois il existe soit des situations encore non prévues par les lois en vigueur, que des points de discussion et de conflit entre certaines positions de l'éthique et les respectives positions en matière juridique et déontologique.

Parmis les problèmes qui attendent encore une réglementation juridique il y a ceux qui concernent l'expérimentation dans le camp des biotechnologies industrielles; en Italie, en particulier, où il n'existe à ce sujet que des propositions et de projets, il faut considérer aussi la matière des manipulations génétiques.

A ce propos deux commissions ministérielles se sont prononcées:

- La Relation Santosuosso (Proposition de discipline de la nouvelle génétique humaine, 22/10/85 ed. Giurisprudenza Italiana 1986, 2, IV, pp. 3-72) exprime avis contraire à propos de l'expérimentation sur les embryons humains, à moins qu'il ne s'agisse de finalités thérapeutiques;

- La Relation Polli sur la Manipulation Génétique (pas encore publiée) fournit des règles en matière de recherche et d'expérimentation en biotechnologie et en génie génétique ainsi qu'en thème de diagnostic prénatal. Il s'agit, toutefois, d'avis n'ayant pas de validité légale.

Pour ce qui concerne les points de conflit, possibles et actuels, entre les règles juridiques-déontologiques et les positions en matière d'éthique, il faut remarquer le thème de l'expérimentation sur embryons humains, surtout à cause de concessions faites en matière juridique-déontologique au regard des embryons précoces avant le 14e jour de vie.

Un autre point de conflit est représenté par la possibilité d'admettre en expérimentation en double aveugle des personnes incapables d'exprimer un consentement valide où auxquelles l'on ne puisse le demander sans troubler ou invalider l'issue de l'expérimentation.

La position de l'éthique personnalistique spécialement dans le domaine de la morale catholique est plus sévère dans la protection soit des embryons en tout stade de développement soit des individus incapables d'exprimer de consentement par rapport aux possibilités de risque et en l'absence de consentement valide et personnel.

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2) BERRI: La revisione della legge sull'assistenza psichiatrica. Quaderni giustizia, 67 et ss. 1984.

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Document 1

ANNEXE I

Lois italiennes en vigueur

Regio Decreto (R.D.) n. 478 du 3.3.1927: Regolamento contenente norme per la produzione e il commercio delle specialità medicinali (Règlement portant les normes concernant la production et la vente des médicaments).

Legge n. 458 du 26.6.1967: Trapianto di rene da vivente (Transplantation des reins entre donneurs et receveurs vivants).

Legge n.431 du 18.3.1968: Provvidenze per l'assistenza psichiatrica (Mesures concernant l'assistan psychiatrique).

Legge n.475 du 2.4.1968: Servizio Farmaceutico (Mesures concernant la vente des médicaments dans les pharmacies).

Legge n. 519 du 7.8.1973: Competenze dell'Istituto Superiore di Sanità (Buts et finalités de l'Institute Supérieur de Santé).

(Suite de l'ANNEXE I)

Circolare Ministeriale n.35 du 9.4.1975
Circolare Ministeriale n.77 du 6.9.1975

Istruzioni concernenti l'autorizzazione al passaggio dalla sperimentazione animale alla sperimentazione umana di un nuovo farmaco. (Instructions concernant l'autorisation à l'expérimentation humaine d'un nouveau médicament après expérimentation sur les animaux) (*).

Legge n.644 du 2.12.1975: Disciplina dei prelievi di parti di cadavere a scopo di trapianto terapeutico e norme sul prelievo dell'ipofisi da cadavere a scopo di produzione di estratti per uso terapeutico (Réglementation des prélèvements de substances humaines des personnes décédées à fins de transplantation thérapeutique et normes sur le prélèvement de l'hypophyse des personnes décédées à fins de production d'extraits à but thérapeutique).

Decreto del Presidente della Repubblica n.803 du 21.10.1975: Regolamento di Polizia mortuaria (Réglementation des enterrements).

(*) Les Circolari Ministeriali n'ont pas de valeur juridique erga emnes, voir ne sont pas des lois au sens propre du terme.

(Suite de l'ANNEXE I)

Decreto del Presidente della Repubblica n.409 du 16.6.1977: Regolamento d'esecuzione della Legge n.644 del 2.12.1975 (Normes pour l'application de la Loi n.644 du 2.12.1975).

Legge n.194 du 22.5.1978: Norme per la tutela sociale della maternità e sull 'interruzione volontaria della gravidanza (Normes sur l'interruption volontaire de la grossesse).

Legge n.833 du 23.12.1978: Istituzione del Servizio Sanitario Nazionale (Création du Service Sanitaire National).

Normes du Code Civil et du Code Pénal; normes Constitutionneles (art.32).

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ANNEXE II

EXPERIMENTATION SUR LES EMBRYONS

La position des différentes confessions religieuses

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1. Eglise anglicane (Comité de Responsabilité Sociale du Synode Géneral de l'Eglise d'Angleterre).

Le Comité n'a pas trouvé d'accord unanime au sujet de la possibilité d'expérimenter sur l'embryon humain. En thèse générale, les membres du Comité considèrent licite l'expérimentation seulement avant la formation des caracteristiques humaines: cette limite est le 14eme jour à partir du moment de la conception, juste au moment de la formation de la ligne primitive.

Les embryons à utiliser doivent être en surplus et non pas conçus en fonction de la recherche.

- GENERAL SYNOD (Report by the Board for Social Responsibility), Evidence to the DHSS (Warnock) Inquiry into Human Fertilisation and Embriology, London, march 1983.
- BOARD FOR SOCIAL RESPONSIBILITY, Human Fertilisation and Embriology. The Response of the Board for Social Responsibility of the General Synod of the Church of England, to the DHSS, Report of the Committee of Inquiry, London, november 1984.

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2. Eglise Anglicane (Synode Général de l'Eglise d'Angleterre).

Le Synode Général refuse d'appuyer la recherche pour des thérapies alternatives de la stérilité et s'oppose à la création d'embryons seulement à fins éxpérimentaux.
Ces décision sont en désaccord avec celles du Board for Social Responsibility (of the General Synod).

- EGLISE ANGLICANE (Synode général de l'Eglise d'Angleterre) Déclaration du 12/2/1985.

3. Conseil Mondial des Eglises

L'équipe de travail n'affronte pas directement le problème de l'expérimentation sur embryons.
Neanmoins dans l'Appendice II ("When does individual human life begin?") l'équipe de travail se questionne sur le moment où commence la vie humaine et conclue qu'il est impossible d'établir scientifiquement le moment précis où l'embryon devient homme: ce genre de résponse ne peut venir que de la théologie.

- CONSEIL MONDIAL DES EGLISE (Manipulating life: Ethical issues in genetic engineering, Geneve 1982)

4. Eglise Evangélique Allemande

Pour l'Eglise Evangélique Allemande la vie humaine commence au moment de la conception: l'embryon humain, en effet, est déjà déterminé en tant qu'individu unique et qui ne peut être répété.

Pour cette raison la vie humaine exige de ne pas être manipulée déjà dès son début et la recherche sur les embryons est, en matière d'éthique, inacceptable.

On ne peut prévoir, en outre, si à l'avenir on pourra considérer licite d'intervenir sur embryons dans des buts exclusivement thérapeutiques.

Avant d'investir des ressources culturelles et économiques dans la recherche sur embryons humains, il faut évaluer l'être en accord avec l'éthique de telles interventions.

- EGLISE EVANGELIQUE EN ALLEMAGNE (EKD), Respecter la dignité de la vie humaine en devenir, dans La documentation Catholique, 16 mars 1986, n.1914.

5. Juifs

Pour pouvoir établir la licéité des techniques de fécondation artificielle, il faut les évaluer suivant les enseignements bibliques: si les techniques en question contreviennent à ces enseignements, ou peut parler d'infraction, autrement, on est libres d'utiliser les découvertes scientifiques pour franchir les obstacles posés par la nature.

Pour ce qui est, en détail, de l'expérimentation sur embryon, chaque vie innocente a une valeur infinie et ne peut être sacrifiée à la science même si dans le but de sauver des millions d'hommes à l'avenir.

- Déclaration de I.Jakobouite, Rabbin Chef de Grande Bretagne sur le Rapport Warnock, 1984.
- D.Bleich, Ethical concerns in Artificial Procreation: A Jewish Perspective, (Academy of the Kingdom of Marocco, 27-29 novembre 1986).

6. Islamiques

En Islam il n'y a aucune limitation de la part de l'Etat au regard de la recherche scientifique. L'homme ne peut être soumis au risque de subir des dommages ou des lesions permanentes du corps sans qu'on considère ses nécessités thérapeutiques eu trayant profit de son état de nécessité.

Les méthodes de recherche et les applications des relatives découvertes scientifiques ne doivent pas pousser l'homme au péché en commettant des actions interdites par la religion islamique.

Les médecins ont le droit et le devoir de participer activement à la conception et à l'approbation de décrets religieux en ce qui concerne la légalité et l'acceptabilité des résultats qui peuvent être acquis dans le camp de la biologie au moyen des recherches scientifiques présent et futures.

De tels décrets doivent être formulés avec le consentement de musulmans experts dans les domaines légal et biologique, qui se rassemblent pour discuter le problème en question.

Pour les cas non prévus par la loi, la règle à suivre est le principe islamique: "Où que soit le bien-être, là sont respectées les lois de Dieu".

- Déclaration du Kuwait: Code islamique d'éthique médicale, Jauvier 1981.

EGLISE CATHOLIQUE - Expérimentation sur l'homme

Les sources et les références officielles, pour ce qui concerne les orientations générales en thème d'éthique catholique à propos de l'expérimentation sur l'homme, sont constituées par les discours des Souverains Pontifes, et en espèce Pie XII, Paul VI, Jean-Paul II, Pontifes qui ont eu occasion d'aborder ces thèmes.

- PIE XII: Discours aux participants au I Congrès International d'Histopathologie du Système Nerveux sur" Les limites morales des méthodes médicales de recherche et thérapie" du 14 septembre 1952.

• La personne humaine est la valeur prioritaire et fondamentale soit à l'égard de la science que de la société.

• Le patient "n'a pas le droit de disposer de son intégrité physique et psychique pour des expérimentations et recherches médicales, loreque de ces actes dépendent, à l'imédiat ou ensuite, destructions, mutilations, blessures ou de graves dangers (principe de totalité).

- PIE XII, Discours à la XVI Session du Bureau International de Documentation de Médecine Militaire du 19 octobre 1953.

Le principe-valeur de la socialité est fondamental dans le domaine de l'expérimentation sur l'homme: l'individu peut se soumettre à un risque pour le bien commun,à condition qu'il le fosse librement et qu'il ne touche pas à son intégrité physique et psychique.

- PIE XII: Discours à la VIII Assemblée de l'Association Medicale Mondiale du 30 semptembre 1954.

Les limites posées à l'expérimentation sur le patient, sur le mourant ou sur le volontaire en bonna santé sont valables aussi dans le cas d'expériméntation du médecin sur son propre corps.

- PAUL VI: Discours à l' XI Congrès National de la Société Italienne de Pathologie du 31 octobre 1969.

Le principe qui doit mener le médecin dans la recherche expérimentale est l'utilisation au mieux de celle-ci pour le bien de l'humanité.

- JEAN-PAUL II: Discours aux participants à deux Congrès de Médecine et Chirurgie du 27 octobre 1980.

"La connaissance scientifique a ses propres lois auxquelles s'en tenir. Elle doit, toutefois, reconnaître une limite invalicables dans le respect de la personne et dans la sauvegarde du droit à vivre de façon digne d'un être humain".

L'expérimentation sur le patient ne peut être conduite qu'après consentement préalable et informé et doit être finalisé à l'intérêt de l'individu et non pas de la collectivité.

- JEAN-PAUL II, Discours à l'Académie Pontificale des Sciences, du 23 octobre 1982.

L'expérimentation sur embryons humains est illicite: "Je condamne de la façon la plus esplicite et formelle les manipulations de l'embryon humain, puisque l'être humain, depuis sa conception jusqu'à sa mort, ne peut jamais être utilisé, en tant qu'instrument, pour aucun but".

- JEAN-PAUL II, Discours au I Congrès Médical du Mouvement pour la vie sur "Diagnostic prénatal et traitement chirurgical des malformations foétales, du 3 décembre 1982.

Il est clair que les recherches endoutérines ayant comme but l'individuation précoce d'embryons ou de foétus torés afin de pouvoir promptement les éliminer avec l'avortement, doivent être considérées viciées déjà à l'origine et, en tant que telles, moralement inadmissibles.

Egalement inacceptable est chaque forme d'expérimentation sur le foétus qui puisse en endommager l'intégrité ou en empirer les conditions, à mains qu'il ne s'agisse d'une tentative extrème de le sauver d'une mort sûre, puisque pour lui aussi reste valable le principe général qui interdit d'utiliser un être humain en tant qu'instrument au profit de la science ou du bien-être autrui.

- S.Congégation de la doctrine de la foi, Instruction sur le respect de la vie humain a naître et la dignité de la procréation, Rome, le 22 février 1987 (pas ancore publié).

DISCUSSION: Gunther Patzig

I regret that Prof. Sgreccia is not here to reply to the comments on his views. Professor Sgreccia has given in his paper a comprehensive picture of the large field which we are going to survey in our discussions. I find myself in general sympathy with his approach (but the emphasis is on "general"). It may be helpful for our discussion to single out some special problems he refers to in his paper and to point out some difficulties and some possible alternatives to his views.

I first want to offer some comments on the four models of bioethics Professor Sgreccia has outlined, which are:

a) Emphasis on the freedom of research with unlimited trust in the control mechanisms of the scientific community and its ability to check dangerous and morally objectionable developments and practices;

b) Affirmation of the priority of the benefits to the society as a whole over the interests and liberties of individuals;

c) Ethical relativism, with the hope that ethics committees on a national or local basis will find a consensus reflecting the prevailing moral view or views of the community in question; and

d) An approach based on the conviction that dignity, liberty and responsibility of each individual person must rank higher than the freedom of research and the interest of society.

Professor Sgreccia firmly endorses model (d) and deduces from this the following fundamental norms: rigorous examination of risk/benefit ratios, the necessity of informed consent in all non-therapeutic experimentation, a complete ban on non-therapeutic experiments with the mentally ill or with minors and especially a complete ban on experiments with embryos.

I think that most experts who have given thoughts to these matters would subscribe in principle to model (d), but I doubt whether most would accept all the conclusions. There are responsible doctors and specialists in bioethics who accept model (d), but who would also accept therapeutic and non-therapeutic research with the mentally ill or with children, provided their legal representatives agree after assessing the benefits and risks.

There is, of course, a moral doubt, whether any third person may sacrifice the well-being and chances of health of someone for whom he is responsible. Many believe that only individuals themselves can sacrifice their own interests. There are also responsible people who accept under strict limitations experimentations with embryos, provided they are produced for implantation and not for research and that they are not kept alive for longer than fourteen days after fertilization.

These divergences may be explained mainly by different conceptions of values as a basis for moral norms. Monsignor Sgreccia refers to the "valeurs inhérentes à la personne humaine", I take it that by this formulation he means that these values are absolute. This is a respectable view, but it cannot be supported by purely rational argument. Values can be rationally defined only as correlates of needs, interests and wishes which sentient beings in general have or might have. According to this view, it is not the value of human life and physical integrity as such, but the fundamental interest that human beings generally have in their own existence, health, autonomy and personal dignity and that of their next of kin and their friends which create obligations to respect values.

On this basis the rights of embryos are not something given, but a moral construction which makes use of the concept of the potential person, a potential bearer of interests, wishes and needs. This concept of the potential person, however, has its own philosophical difficulties.

Professor Sgreccia is aware of the fact that not all moral norms can reasonably be codified into civil or penal law. He insists, however, that some fundamental norms of bioethics must be incorporated into national and international legislation: the sanctity of human life, the exclusion of any exploitation of humans by other humans and the right of doctors and other medical professionals to refuse to take part in practices allowed by law that are against their moral convictions. These are reasonable, or at least debatable, proposals. The first principle, the sanctity of life and physical integrity, is in effect written into the constitution of my own country (article 2, paragraph 2 of the Basic Law of the Federal Republic of Germany).

Apart from these very general principles, I share with many others grave doubts concerning the wisdom of regulating questions of medical ethics by law. How to assess the amount of risk to which a patient may be exposed in order to reach new important knowledge is a problem which law cannot resolve. Even ethics committees will have difficulties in some cases.

The role of ethics committees must also be looked at in the light of the fact that there is a tendency to have recourse to formal procedural rules where it is difficult or even impossible to find convincing norms for decision. In Germany, over the last years, many such ethics committees have been constituted mainly as a consequence of the rules adopted by our National Science Foundation, ("Deutsche Forschungs- Gemeinshaft") not to fund any research project involving experimentation with human beings or animals without recommendation by an Ethics Committee. The founding of Ethics Committees in Germany is, I must confess, rather far behind that in countries like the United Kingdom, Canada and the United States.

If too many things are regulated by laws and by procedural rules, awareness of personal responsibility of doctors and other researchers may be reduced. It should be kept clear that the responsibility rests with the individual doctor and scientist. The law should and can provide a general frame of reference. Ethics committees have a valuable function in raising the level of consciousness concerning moral problems in the medical profession and the scientific community in general. They may also, by rational discussion of all relevant arguments, make it easier for doctors and researchers to come to morally acceptable decisions. If doctors and researchers would come to think that everything is all right as long as they conform to the law and get approval from their respective ethics committees, we might in the long run lose more than we can possibly gain.

Document 2

SHARING THE RISKS: THE MANAGEMENT OF RESEARCH
PARTAGE DES RISQUES: LA GESTION DE LA RECHERCHE

Per Juul

Discussion: Vittorio Sgaramella

Session C / Séance C

International Summit Conference on Bioethics
Colloque international de bioéthique

Sharing the Risks: the Management of Research

PRESENTATION: Per Juul

Introduction

The following personal statements, comments and questions result mainly from working in national and international drug regulatory authorities as a medical pharmacologist. They do not represent any theoretical considerations of bioethics. They do not constitute a catalogue of risks or solutions to problems, but are meant to be topics for consideration and discussion.

Discussion of biomedical ethics in connection with research on human subjects are closely related to "risk." This relation is based upon experiences from the past and partial discontent with the present "state of the art."

By way of introduction it should be stated that the risk of the vast majority of investigations in humans is indeed very small.

It may furthermore be appropriate to state that ethics/risk of biomedical research are closely related to the demands by the society of "progress" - in competition with other resource - demanding activities, and that economics (society, industry, investigators) to a large extent influence the risks accepted and hence the "ethics."

Basically ethics must build on the attitude of the public, since ethics are the reasoned analysis of moral behaviour, the study of compunction. The rules, regulations and recommendations worked out by national, international and supranational regulatory authorities, governments, politicians and professional organizations must reflect the public attitude, which for numerous reasons may be as emotional as the attitude of politicians and professionals in other particular matters.

> Most of the ethics/risk problems dealt with concern less than one fifth of the world population, and millions of patients and volunteers in the developing world would benefit from participation in even "high-risk" biomedical research - and would gladly do so without informed consent.
>
> A statement of a prisoner to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1975) should be quoted (1): "You are in a place where death at random is a way of life. We have noticed that the only place in this prison that people don't die is in the research unit. Just what is it that you think you are protecting us from?"
>
> The tremendous horror in the Western world of the AIDS - epidemic (now comprising approximately 35,000 patients) supported by part of the medical profession and the lay press to a surprising extent rapidly ensured vast resources for research - in a striking quantitative contrast to the resources spent on the classical areas (cardiovascular and malignant diseases, traffic accidents et cetera). "Ethics" were rapidly changed by fear.

It may seem immediately intelligible that the attitude of the legislation, guidelines and declarations should reflect the concepts of society - positive ("thou shalt") as well as negative ("thou shalt not"). However, "who" is "society"? In most introductions to papers on ethics issues the differences and controversies caused by different historical, cultural, political, economical, social, religious and personal conditions are emphasized, but it is thought-provoking that even between closely related countries (e.g. the Nordic countries) and between countries trying to harmonize for decades (e.g. the EEC countries) differences as to the evaluation of ethical problems do exist.

In professional discussions of ethics the contact with realities is often lost and the proportions distorted. The paper by Cohen: "The case for the use of animals in biomedical research" (2) is worthwhile considering - whether one agrees with the author or not.

"Sharing the risks: the management of research" - in the strict sense an impossibility when considering the individual subject in a research project - is a provoking title of a paper when extended to cover healthy volunteers/patients, non-therapeutic/ therapeutic research, national/international cooperation (including developing/developed countries), economic responsibility (society/industry), legal/insurance/liability matters and responsibilities of investigators/industry/regulatory authorities/society.

Many of the problems discussed in this paper are mentioned in the recent draft "Recommended basis for the conduct of clinical trials of medicinal products in the European Community" (3).

"The risk management process can be conceived as consisting of the following components: hazard identification, risk estimation, risk assessment, determination of propensity for risk acceptance, analysis of benefits, disbenefits and alternatives. Hazards are defined as a set of circumstances with a potential for causing harm. Risk is the extent of harm and the probability of its occurrence" (4).

Risk

As is it stated above the evaluation of risk in a research project and/or therapeutic situation is absurd without considering the possible benefit to the research subject or to others. Furthermore, even a benefit/risk ratio in itself is meaningless unless compared to the ratio of an existing and relevant alternative. When considering biomedical research the benefits are unknown - otherwise the investigations may be considered unjustified and hence unethical. The risks may be wellknown, reasonably estimated or completely unknown. Even if the risk is statistically known, "the public does not understand risk" (5). This lack of comprehension may be explained by insufficient knowledge of the layman of mathematical expressions, statistical and epidemiological calculations et cetera or an insufficient way of being explained the risk in understandable terms. However, one may speculate whether statisticians, medical professionals and politicians do understand the actual meaning of "risk" and "relative risk" and are able to interpret these statistical concepts in relation to the public and to the individual.

> An incidence of a lethal adverse reaction to a drug of 1:100,000 treated patients by most physicians will be considered a very low (and acceptable) risk. By the one out of 100,000 dying from the adverse reaction (or his bereaved) it may be considered completely unacceptable, particularly if the drug was prescribed for a non-serious disease.
>
> The average American loses 1.19 years of life expectance due to accidents and about 0.25 years from improper use of drugs in medical treatment (5). Do these data mean anything? Perhaps to the economist and politician, but certainly not to other people: The numbers cover a loss of perhaps 70 years of a baby and 10 minutes of an old man. Accidents are accepted as being unavoidable, which is not the case concerning drug disasters.
>
> "A chance of a fatal accident while driving, cycling, busing, taxiing or walking to the general practitioner's surgery to collect a prescription exceeds by several orders of magnitude the risk that anything written on the prescription will kill you" (6). And so what?

> A patient with incurable cancer or AIDS will often accept any new treatment despite the information that nothing is known of efficacy and/or adverse reactions. A healthy volunteer probably has rather different points of view regarding adverse reactions.
>
> "A risk greater than minimal is not acceptable for healthy volunteer studies," says the report of the Royal college of Physicians' working party considering research on volunteers (7). What is minimal? A 0.05 per cent risk of a complication following a percutaneous liver biopsy?

The acceptability of risk is even more complicated. Starr ("Social benefit versus technological risks" (8)) suggests three "laws of acceptable risk":

1. The acceptability of risk is roughly proportional to the third power of the benefit (i.e. $R=KB^3$ where R is the level of risk, B is the benefit and K is a constant).

2. The acceptable level of risk is inversely related to the number of persons exposed to that risk.

3. The public seems willing to accept risk from voluntary activities (e.g. mounting climbing, skiing or smoking) roughly a thousand times greater than it would tolerate from involuntary activities (e.g. nuclear power, pesticides) that provide roughly the same level of benefit.

Although these "laws" do not directly apply to the research situation and the use of medical intervention including drugs they point to important factors relevant to the activities of regulatory authorities when evaluating clinical trials' protocols and new drug applications.

The absolute number of patients suffering from a particular adverse drug reaction influences the opinion of the public as well as that of politicians and professionals. In the evaluation of the relative incidence, i.e. number of events/number of treated patients compared to the number of events/number of untreated patients, the denominator is often forgotten (examples: phenylbutazone, benoxaprofen, oral contraceptives).

Numerous declarations, rules, guidelines and papers deal with ethical problems involved in human experimentation, among which the most important and generally accepted is the "Helsinki II declaration" (1975). However, in many areas these notes for guidance are not specific, which is a necessary consequence of the topic in question. Their main importance may lie in their statements of attitude towards the individual human being, and it should be emphasized that biomedical research should not only comply with the words of the Helsinki II declaration, but also adhere to the spirit of the declaration (3).

Among recent monographs on the topics of ethics in clinical research should be mentioned Levine (1) and the chapter by Vere in (9).

It may be reasonable to distinguish between therapeutic biomedical research (patients) and non-therapeutic (healthy volunteers or patients with an "irrelevant" disease). A greater risk may be acceptable in the former case, as the patient has the potential benefit from the experiment/trial.

> A high risk of even severe bone marrow depression is acceptable in a phase I trial with a new drug in patients with AIDS or incurable malignant disease.
> A risk of 0.05% following percutaneous liver biopsy in healthy volunteers may be unacceptable.

The risk should be "minimized" in both instances, but apparently to a different extent - and to which extent? The approximate size of the risk may only be known for wellknown procedures and foreseeable events.

The risk indeed is minimal in most cases, and it may very well be that at least in therapeutic research the risk of participation generally is lower than the risk involved in established pharmacotherapeutics.

> In publications covering more than 120,000 research subjects in non-therapeutic investigations 1 death occurred, the major adverse reactions occurred at a frequency of 0.5:1000 and minor adverse reactions at 13:1000.
> In clinical trials comprising more than 11,000 patients 26 deaths occurred which were not considered attributable to the drug in question, major events occurred at a rate of 13:1000 and minor events at 61:1000 (10, 11, 12).
>
> During 1964-76 29,162 prisoners were involved in 805 protocol studies of phase I drug testing (614,534 subject days). Clinically significant medical events occurred in 64 cases (58 adverse reactions and 6 complications). All subjects recovered completely. A 31-year old man died from cerebrovascular haemorrhage while receiving placebo (13).
>
> However, serious and even lethal adverse reactions and complications do occur. A 31-year old apparently healthy volunteer died during a tolerance study of a new antiarrhythmic from cardiorespiratory arrest (14).

The hazards can be considered larger at the initial phase I trials in human volunteers than in later phases, partly because only a limited preclinical toxicological program has been carried out (15). The total animal toxicological program is carried out during clinical phases, i.e. before the application for marketing, but not before the initial phase I studies. This situation is caused by the fact that animal toxicology demands vast resources (time as well as money), and that only a small fraction of drugs entering clinical phases results in marketing.

> Out of 197 chemical entities investigated in man only 18% were finally marketed. Approximately 8% of the compounds were abandoned due to adverse reactions (16).
>
> "Average" figures concerning the number of healthy volunteers and patients in the developing of a new drug are: phase I (healthy volunteers): 100, phases II-III (patients): 1600 (17).

The present scheme of development of new drugs seems to result in the marketing of drugs with an acceptable benefit/risk ratio, as only less than 2% of the drugs marketed within the last 20 years have been withdrawn from the market due to adverse reactions.

The Randomized Clinical Trial

The basic and complex issues regarding the controlled clinical trial and particularly the randomization have been dealt with very little in the various laws. The discussions were intensified in 1979, when a new design for randomized clinical trials was proposed assigning patients randomly to different treatment groups without their prior knowledge and consent (18). The question was asked: what are the rights of patients receiving the control/standard treatment - whether informed consent is obtained or not?

> "A randomized clinical trial of active therapy versus control is an attempt to determine the average benefit/risk ratio in a statistically two-sided situation" (19).
>
> "Perhaps investigators should more willingly admit that the purpose of many trials is to convince, not just to explore" (20).

> "It is of note that many of the major advances in medicine have occurred as a result of serendipity rather than from sophisticated double-blind randomized controlled trials" (21).

Numerous problems exist as to the selection of human volunteers and patients for biomedical research, e.g. concerning children, elderly, females of fertile age, prisoners, students and employees within the pharmaceutical industry. Many official and unofficial guidelines exist on this selection. Although they have the same goal: to obtain the highest ethical standards and minimal risk, they differ in their (often vague) recommendations. However, without the possibility of investigating drug effects in the groups of patients for whom the drug may be later intended, the groups of patients in question shall be "therapeutic orphans."

> In a recent study the decisions of proxies for 168 patients in nursing homes about whether to permit the patients' participation in a study involving minimal risk wee studied. Almost 50% (78/168) refused consent (22).
>
> The problems involved in research on children are even more controversial. They are dealt with in a recent analysis (23).

The use of a reference treatment is the subject for continuous discussion (particularly concerning placebo), and differences between countries may even cause "exportation" of trials.

> Recently a placebo controlled trial of a new antidepressant was being considered "transferred" from Denmark to Sweden, because such a comparison might be required by the Swedish authorities but might be considered unethical by the Danish authorities.
>
> In the Danish Medicines Act (1975) it is stated: "To obtain registration of a pharmaceutical speciality ... it shall, in comparison with specialities already approved, be suitable from a health point of view." This

point of view is not generally accepted in all other EEC countries.

A major ethical requirement for the justification of a randomized clinical trial is a bona fide null hypothesis. However, most often at least preliminary evidence indicates an effectiveness superior to placebo, before a controlled clinical trial is initiated.

With regard to the reference treatment the question must be asked whether this should be the optimal treatment or just a standard treatment - realizing that professional evaluation of "optimal treatment" differs between individual professionals, between "schools" and between countries.

The statistical null hypothesis in itself is an abstraction, since most often equal effects are not looked for or anticipated.

The statistical considerations may give rise to ethical problems: a trial planned to investigate a new drug compared to existing therapy with a cure rate of 80% of the standard drug and a minimal relevant difference concerning the new drug of 10% (90% cure rate) shall require approximately 200 patients in each group (2 alfa 0.05, beta 0.20). If the new drug is compared to placebo with an expected effect of 30%, the number of patients shall be only approximately 10 in each group. Thus the latter design much more rapidly, with few resources and involving only few patients shall give an answer to he question: equal to placebo? However, the answer is of little clinical relevance, as placebo is not the standard treatment, and 10 patients would be exposed to placebo, i.e. deprived of a standard treatment with an efficacy of 80%. In some cases the placebo-controlled design is ethically justified and measures may sometimes be taken to ensure the control group an optimal treatment, but in many cases this is not possible.

Particular problems concerning large scale trials arise with an increasing frequency: use of various drugs in the prevention of acute myocardial infarction, use of estrogens in the prevention of postmenopausal osteoporosis, changing existing antihypertensive therapy to ACE-inhibitors to improve "quality of life" et cetera. Such investigations may require the involvement of tens of thousands of subjects and may last for

> several years with the resulting problems of the establishment of a final benefit/risk ratio.
>
> A particular and increasing problem is concerned with the ethical aspects of large-scale double-blind investigations where there is a high mortality rate among the patients. In the UK a new scheme involving and independent statistical monitor and resulting in a statistical trend analysis during the trial is suggested (24). However, almost any interference with the classical double-blind design may induce bias, which make a correct conclusion impossible and thus render the trial unethical.

Despite all the problems involved in the randomized clinical trial concerning ethics, risk, resources and practice no relevant substitute has so far been suggested. "Clinical freedom died accidentally, crushed between the rising cost of new forms of investigation and treatment and the financial limits inevitable in an economy that cannot expand indefinitely. Clinical freedom should, however, have been strangled long ago, for at best it is a cloak for ignorance and at worst an excuse for quackery. Clinical freedom was a myth that prevented true advance" (25).

It can even be argued that the ideal way of determining the optimal therapy for the individual patient - which may also be considered an experiment - would follow the principles of a randomized trial, a socalled "N of 1" - study (26).

Even when accepting these statements the protection of the scientific integrity of a clinical trial presents ethical dilemmas. In the paper by Howard and Friedman (27) six fundamental conditions are quoted: 1) the number of subjects should be sufficient, 2) a control group should be incorporated, 3) the assignment to the treatment and control groups should be randomized, 4) where possible the trial should be based on a double-blind design, 5) patient withdrawals should be held to a minimum, 6) during the trial the patient should be as free as possible of other therapies. All these six points involve ethical problems, and "sometimes it is impossible to optimize patient care and simultaneously protect the scientific integrity of a trial. It then becomes necessary for physicians to choose between the two conflicting objectives."

The number of research subjects in a trial necessary to reach a statistically significant and clinically relevant conclusion is a particular problem. With regard to the risk the number should be as small as possible, but a too small number makes a final, quantitative conclusion impossible, which renders the trial useless and hence unethical. The latter situation is by far the most common.

The demands by the regulatory authorities on the medical professional and scientific qualifications of the trialist differ between countries, but in most countries only vague statements exist and no control (including Good Clinical Practice) is exerted.

Laws and guidelines. Administration

The above mentioned statements pose numerous questions to the trialist - professional (medical, statistical) as well as ethical and practical.

> If the "investigator" happens to be a young intern or resident being asked to compare the analgesic effects of paracetamol to aspirin in post-episiotomy pain, the anxiolytic properties of a new benzodiazepine to diazepam or the relation between free (protein unbound) plasma concentrations of disopyramide and antiarrhytmic activity, he may find himself entangled in problems concerning the evaluation of preclinical results,

pharmacokinetics and -dynamics, statistics, ambition, ethics and required administrative procedures.

"Society" must provide rules, requirements, regulations, standards, recommendations and guidelines to assist the investigator in carrying out an investigation which - apart from the scientific aspects - ensure maximal benefit with minimal risk to the volunteers/patients involved in the study and adherence to conditions of responsibility (legislation, liability, insurance, ethics).

A practical problem is to ensure that the trialist and the industry are acquainted with the relevant declarations/guidelines and have easy access to them. They comprise a.o. the Helsinki II declaration (Tokyo 1975), the Proposed Guidelines for Biomedical Research Involving Human Subjects (Geneva 1982), various declarations by the World Medical Association (Venice 1983, Tokyo 1975), the Declaration of Hawaii (World Psychiatric Association), numerous laws, rules and guidelines issued by national, international and supranational authorities (WHO, The Council of Europe, EEC, national regulatory and research ethics committees) concerning ethical problems in general and particular patients/volunteers at risk. Probably many trialists and persons working in industry are not acquainted with this enormous collection of papers, the different legal matters (liability) and the conditions of insurance.

Teaching of these matters in medical schools (graduate and post-graduate teaching of clinical pharmacology) should be obligatory. The rules should be collected (as it is the case concerning the rules and regulations of different countries regarding the requirements for the application of a marketing authorization of a new drug) or preferably a revised and comprehensive "Helsinki III" declaration should be prepared.

A typical sequence of events would be that a trials' protocol is submitted to an institutional review board/scientific ethics committee and a national regulatory authority.

The scientific ethics review board in many countries is mainly geared to deal with matters of risk/ethics. However, laymen having an evident role in these matters may have difficulties in evaluating professional matters (animal experiments, pharmacological and clinical details et cetera). Furthermore the boards may not discuss all notifications/applications - exceptions being cases where the investigator claims to adhere to the Helsinki II declaration ("self-declaration").

> In 1985, 1301 notifications were considered by the regional scientific ethics committees of Denmark. A detailed evaluation was only made in 106 cases (approximately 9%). The reasons for a detailed evaluation were: special circumstances where informed consent had been partially or totally dispensed with, request from investigators for an evaluation and evaluation deemed relevant despite self-declaration. Ninety per cent of the projects involved patients and 10% volunteers (28).

The national drug regulatory authorities may deal with research projects as applications or notifications (according to the respective medicines acts) with major differences between countries. As a rule only trials involving drugs are involved. In some countries phase I studies (normally carried out in healthy volunteers) are excluded, in other countries phase IV studies (postmarketing studies) are not covered. In probably all countries the resources for the administrative and professional handling of the notifications/applications are limited.

> In Denmark (5 million inhabitants) approximately 600 notifications of clinical trials are considered annually by the National Board of Health. The total number of

healthy volunteers/patients enrolled is approximately 30,000.

International cooperation

In a broad sense risk may sometimes be shared internationally, and unnecessary repetition of biomedical research is unethical.

It may be advisable to include in the WHO Emergency Health Kit an oral antibiotic which can be administered once daily. Normally these antibiotics, e.g. co-trimoxazole and co-trimazine are administered twice daily, but from a kinetic point of view at least the latter might be administered at a once a day schedule. This hypothesis should be investigated before releasing the dosing schedule for uncontrolled use in thousands of patients under emergency situations, e.g. catastrophes. Such a trial cannot be performed under the clinical situations in question. Would it be ethically justified to let patients of a Western country under normal clinical control share the risk by participation in a randomized clinical trial?

Some countries have consistently asked for clinical data originating in their own country. This may in certain instances be justified or at least understandable, but it must usually be considered unethical (29).
The US Food and Drug Administration has for the first time in its history approved an IND (Investigational New Drug) for a new anticancer drug based on European clinical data, an important step ahead (30).

Delay in the introduction of sodium valproate into the US market has been estimated to have subjected American patients to approximately one million unnecessary seizures a year at a cost of approximately $ 200 million a year. Delay in the introduction of suitable anti-arrhytmic agents has been estimated to cost 10,000 deaths a year in the United States (31).

Is it ethical to conduct in vivo bioavailability studies in healthy volunteers/patients to ensure bioequivalence of a generic equivalent, the relevance of which only concerns the price? Does it change the evaluation of ethics, if the product in question is intended for the use in developing countries as part of the WHO Essential Drugs Program?

Exportation of clinical trials, lack of information of previous or simultaneous trials in other countries, lack of information of the reasons for carrying out clinical trials in countries other than that or origin and non-acceptance of foreign data (even when of acceptable quality) are major ethical problems which might seem to be solvable.

Economy, responsibility, liability and insurance

Only 10-12 out of 20,000 new chemical entities reach the stage of clinical trials, and only 1-2 out of these reach marketing. The total time of development of a new drug may be 15 years and the total cost may amount to 100 million US $. The risks and resources spent are enormous, and the responsibility for the overall development of new drugs (and other therapies) perhaps in some way ought to be shared by the drug industry and "society", the latter to the final end paying the bill (patients, reimbursement et cetera). Society should assume the superior responsibility concerning medical research (32).

> Should a "no-need clause" as it is practiced in Norway be more generally adapted?
>
> Should national authorities actively encourage and support the development of certain drugs, e.g. "orphan drugs" so far only adopted by the FDA?
>
> Is it ethical to allocate resources to clinical trials of analogous drugs within therapeutic areas with existing acceptable therapy (e.g. nonsteroidal antinflammatory drugs, anxiolytics, topical glucocorticosteroids, beta-receptor blocking agents and antihistamines), when the resources must be taken from other health activities? ("One man's provision another man's deprivation").

> Should society take particular responsibility concerning trials of expected particular benefit?
>
> Is it ethical to accept "marketing trials", i.e. trials with the main purpose of advertising - often multicentre-trials of limited value?
>
> A theoretical calculation suggests that it could cost as much as 55 million per life saved if measures were taken to monitor extensively the use of every new medicine introduced. " 55 million spent on health education in the prevention of heart disease, for example, could probably save hundreds and perhaps thousands of lives" (33).
>
> Industrial representatives of a consensus conference 1984 supported and academics rejected, that a multicentre trial can be justified simply by the wish to speed drug registration (34).

The economical aspects of carrying out clinical trials are normally dealt with to a limited extent in the official notifications/ applications to scientific ethics committees and drug regulatory authorities: cash payments for research subjects, payments for technical elements (analyses, secretary assistance, instruments) and economical engagement with the investigator (cash, expenses in connexion with congress participation, research funds et cetera).

Matters concerning insurance of the research subjects and liability problems similarly may not be dealt with.

> In Denmark this information is not required. In the final draft for the EEC paper concerning the conduct of clinical trials (3), however, it is stated that this information "should be clearly apparent".

The information to the investigator concerning legal responsibility and liability is especially important as these matters are often very difficult to comprehend to non-lawyers.

The responsibility for a clinical trial is shared between the investigator, the manufacturer and "society". The investigator is responsible for the professional medical aspects of the trial (including ethical aspects). The manufacturer is normally responsible according to product liability. Society is normally only economically responsible insofar as damages are covered by general laws and rules (e.g. comprising hospitals and clinics). The different national laws and regulations may be difficult to understand, which is also apparent from the results of legal cases.

The basic factor concerning liability is the "culpa" principle (the injury is caused by a fault or negligence by the trialist and/or manufacturer). A developmental damage results from an injury that could not and should not have been known (recognized) at the time of trial/treatment. A system damage is the result of a known, but in the individual situation unavoidable risk. These matters similarly are of importance concerning insurance.

> A quantitatively minor, but occasionally important point is the co-signature by the manufacturer of the application/notification to the authorities. The manufacturer for various reasons may choose not to sign a trials protocol. In these cases his responsibilities are only covered by ordinary product liability. The regulatory authorities may reject such a trial - or the trialist may seek other ways of obtaining the necessary economic insurance.

Insurance principles and rules vary from country to country. They may either build on the culpa principle (the claimant must prove that a fault was the cause of the injury) or on strict liability administered by the law courts (the claimant must prove that a causal relationship exists between research method and injury) or on "no fault liability" (strict liability, administered by a special board and financed by public or private means). The latter possibilities are favoured in the Proposed International Guidelines for Biomedical Research Involving Human Subjects (Geneva 1982), are operating in some countries, e.g. New Zealand and Sweden, but not in other countries, e.g. the United Kingdom (35). Even in the case of strict liability the claimant must prove a causal relationship between the treatment/trial and the injury ("beyond reasonable doubt"), and a longlasting legal process cannot be excluded.

> A new Danish law concerning insurance of patients in general and considering drugs in particular shall include problems concerning research subjects. A "no fault" liability is suggested, and the insurance shall be financed by public as well as private means. The intentions are to strengthen the legal status of the volunteer/patient and to speed up the administrative/legal process. The total expense is estimated at 10-15 million US $ (total Danish population 5 million).
>
> In Denmark only 1 case of possible injury in connexion with biomedical research has been taken into court within the last 10 years (during which period 300-500,000 subjects have participated in research projects). A staphylococcus aureus pneumonia/pleuritis occurred in a volunteer after intravenous infusion of amino acids. The volunteer lost the case in supreme court. It is furthermore noteworthy that the trial took place in 1976, whereas the final legal decision in supreme court was taken in 1985, i.e. after a period of 9 years, which seems an unacceptable and unethical length of time.

Discussion, comments and conclusions

It is reasonable that risks concerning economic, professional medical, liability and insurance matters are shared between investigator, manufacturer and society - even if this may result in a weakening of responsibility. It is equally important that these matters are dealt with openly (publicly) and that internationally harmonized rules and regulations are developed.

The risks of harm/injury/damage (physical and mental) to the research subjects are indeed very small. Their existence must be realized and evaluated according to the project in question, but they should not be over-emphasized. Forty years of continuous discussions have improved the professional - including ethical - standards of biomedical research.

The major "risk" with clinical trials is that they are often planned and carried out in such a way that no clinically relevant and statistically significant conclusions can be arrived at. One reason for such trials is the incompetence of the trialist resulting in an inadequate protocol. Another reason is that many trials are terminated before completion due to causes unrelated to the investigation.

The superior responsibility of society with regard to its possible influence on the development (progress) balanced by the necessity for giving priorities is the most important and the most difficult to handle - difficult because it is a result of political and economic interests in health matters of interest to the public as well as to the individual. Unfortunately we are not able to furnish governments and politicians with the most necessary information concerning drug utilization - being part of a general technology assessment.

The respect for human life gradually shifts to the respect for human dignity and quality of life. The respect for the individual must be without compromise - but the individual does not exist independently of the surrounding society: risk and responsibility must be shared.

In the Appendix a few topics for discussion are stated.

Epilogue

Leo Szilard's Ten Commandments (1964) (1)

1. Recognize the connections of things and the laws of conduct of men, so that you may know what you are doing.

2. Let your acts be directed towards a worthy goal, but do not ask if they will reach it; they are to be models and examples, not means to an end.

3. Speak to all men as you do to yourself, with no concern for the effect you make, so that you do not shut them out from your world; lest in isolation the meaning of life slips out of sight and you lose the belief in the perfection of the creation.

4. Do not destroy what you cannot create.

5. Touch no dish, except that you are hungry.

6. Do not covet what you cannot have.

7. Do not lie without need.

8. Honor children. Listen reverently to their words and speak to them with infinite love.

9. Do your work for six years; but in the seventh, go into solitude or among strangers, so that the memory of your friends does not hinder you from being what you have become.

10 Lead your life with a gentle hand and be ready to leave whenever you are called.

APPENDIX

Topics for discussion

a) Should "society" have a greater insight in/influence on/ control of drug development (e.g. therapeutic analogues and generic equivalents) - or is the mere threat of a "no-need clause" irreconcilable with the freedom of thought, research and trade?

b) Should "society" encourage and support the development of "orphan drugs" and "essential drugs"?

c) Should "society" assume an increased economic responsibility concerning the research of drug development?

d) Should a collection and comprehensive publication of relevant international declarations and guidelines concerning the issues of ethics, responsibility, liability and insurance be encouraged - or a comprehensive revised "Helsinki III" declaration developed?

e) Should national acceptance of foreign data (provided of acceptable quality) be encouraged?

f) Should the "exportation" of clinical trials be diminished (e.g. by requesting the reason(s) for carrying out the investigation in another country than that of origin of the drug?

g) Should increased teaching concerning ethics / risk / responsibility / liability / insurance issues be recommended as obligatory elements in the graduate and postgraduate teaching of clinical pharmacology?

h) Should information concerning economics, responsibility, liability and insurance be included in notifications/ applications of biomedical research projects?

i) Should a definition of "minimal" risk concerning investigations in healthy volunteers be attempted (e.g. a risk of 1:100 concerning minor events and 1:1000 concerning major events (non-fatal; not resulting in permanent injury))?

j) Should a harmonization as to the requirements of placebo-controlled trials be attempted?

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DISCUSSION: Vittorio Sgaramella

The experimental use of drugs, devices or treatments involves risks for at least three categories of individuals: a) the subjects/patients; b) the researchers; c) the manufacturers or producers. But it should be borne in mind that the alternative to controlled experimentation is simply the lack of such experimentation: in this case, the use of untested or badly investigated treatments, or the loss of a new, potentially worthwhile intervention would clearly expose mankind as a whole to much greater risks than those ensuing from carefully planned and controlled research. It may therefore be appropriate to add the whole of mankind to the list of those at risk in research involving human beings.

The greatest risk is that to which the category of subjects and patients are exposed. Subjects may include healthy persons who for humanitarian or economical reasons voluntarily agree to participate in a clinical trial of an innovative treatment. Animal models and, even better, computer based simulations should be used to reduce the participation of healthy volunteers to a minimum. It is nevertheless clear that their role and contribution remain essential. It follows then that the highest care should be given both to minimize their exposure to risk, and to provide them complete preliminary information as well as prompt updating on possible untoward consequences of the treatment.

Conversely, the submission of patients to experimental procedures raises the issue of voluntary consent. The almost total dependence of the patient on medical advice, as well as the difficulty for patients to understand the intrinsic complexities of experimental protocols, are unavoidable conditions which limit, if not erode, the validity of voluntary and informed consent.

Every effort should be undertaken to reduce the risks of harm to subjects/patients. It should be mandatory that any research involving human beings be discussed and approved by institutional bioethics review committees. In addition, normally every subject should be given in advance a written form which describes in easily understood language the nature of the experiment and the possibility that it can be interrupted at any time by the subject or by the researchers and which describes provisions for compensation in case of injury. Written approval should be obtained from the subject/patient or from a relative or legal guardian. Although in some cases cumbersome, such an operation should ultimately improve the whole process of experimenting "on", or rather "with", human subjects.

As for the share of risk assumed by the researcher, it is unfortunate that the professional sanctions imposed for possible wrongdoings are inadequate. On the other hand, an excessively easy access to court by the subjects/patients or their representatives in case of negative results, and an indiscriminate liability of the researchers are likely to paralyze any experimental effort. A healthy balance between an expert, possibly external, check and an understanding attitude towards the intrinsic unpredictability of any experimental effort, is the primary goal of the ethical review process.

Coming finally to the risks experienced by the drug or device manufacturers, while it is undeniable that they exist, and that they should not be exacerbated, it is also obvious that among the three groups at risk, they are the least vulnerable.

Nevertheless a more direct involvement of the manufacturers in research could certainly be envisaged and possibly formalized.

Document 3

WHO SETS STANDARDS FOR WHAT AND HOW?
LES NORMES: QUI DETERMINE QUOI ET COMMENT?

Paolo Fasella and Umberto Bettazzoni

Discussion: Liborio Falanga

Session D / Séance D

International Summit Conference on Bioethics
Colloque international de bioéthique

Who Sets Standards for What and How?

PRESENTATION: Paolo Fasella and Umberto Bertazzoni

> Why has the nightmare, which I had projected into the seventh century AF (After Ford) made so swift an advance in our direction? The answer to these questions must begin where the life of even the most highly civilized society has its beginning - on the level of biology. (A. Huxley, Brave New world Revisited, 1959).

The time-honoured belief that medicine is engaged in promoting the welfare of people and that research is necessary to this process, is generally accepted. Nevertheless, society is now more aware of the perils inherent to experimentation and is not willing to endorse medical research which is not ethically justified. Experimental medicine entails profound responsibilities which cannot be solely left to the judgement of the persons assigned to it. It is clear that research with human subjects must be constantly confronted with bioethical principles.

The approaches to such problems are strongly dependent on cultural, social and religious conditions as well as on S/T development. This diversification of approaches must be recognised and respected. However, because of the increasingly intense exchanges among the various peoples of the world, including exchanges which involve industrial competition in the pharmaceutical and biomedical field, it becomes extremely important to define some common basic regulations and to set widely acceptable and accepted standards. In the past 40 years, society has succeeded in establishing general principles and in consolidating ethically acceptable protocols which are followed by the great majority of industrialized countries. The translation into practice of these principles is still a formidable task and international cooperation is needed to achieve a general acceptance of normalized criteria and controls. The precise definition of standards is dealt with in other contributions. Here I shall use a broad definition of standards as those sets of rules which should be followed in order to satisfy the requirement of ethics in experimentation on man. The technical problems found by medicine are as old as medicine itself. We shall confine ourselves to development since the end of World War II.

Who sets the Standards

The ethical problems posed by medical research are as old as medicine itself. We shall confine ourselves to some main developments since the second World War.

The necessity to protect the human subject was solemnly affirmed by the Nuremberg Code (1947) and recognised in more specific terms by the Helsinki (1964)/Tokyo (1975) declarations of the World Medical Association (cf. Table 1). As a result of, or with reference to these statements, a number of recommendations were expressed by various agencies and institutions and a number of Ethics Committees were set up to advise on and supervise clinical experimentation.

In some countries this process followed a spontaneous approach while in others it obeyed centralized directions. Thus, bioethics standards have been set by very many different agents ranging from individuals to institutions, to learned and professional Colleges or Councils, to regional and national authorities, to international and intergovernmental organizations. The various sets of standards reflect the needs, customs, cultural, social, political and religious conditions of the proposing agent.

An important step towards internationally accepted standards for medical research was made in 1982 by the Council for the International Organizations of Medical Sciences (CIOMS) and the World Health Organisation (WHO) by the publication of the document "Proposed International Guidelines for Biomedical Research Involving Human Subjects". This was followed in 1983 by the "Safety Requirements for the First Use of New Drugs and Diagnostic Agents in Man".

These documents provide a reference for the standards to be followed in experiments on humans including early clinical trials. An important point is that the objectives of such experiments (outlined in Table 1) should be correctly identified. These general recommendations are usually enforced by different means: ranging from legislative provisions to guidelines. Many differences exist among the various countries both for what concerns the specific requirements (such as methods to be followed, protocols for obtaining informed consent, ethical terms of reference, etc) and the nature of the adopted standards. In some cases these are established by governments, in others by local authorities or professional bodies or institutions. While some delocalization generally favours effectiveness and efficiency, it is highly desirable that the competent authorities of each country be informed of any medical research on humans going on within their territories, that the modalities and the contents of the notification be properly defined and that any abuse be prosecuted or vigorously discouraged through a variety of means, including the control of research grants and publications.

A representative list of the institutions responsible for setting standards in various countries is presented in Table 2. It is clear that the approaches vary in a substantial way. The setting up of ethical Committees is largely recommended although their distribution is rather uneven: committees have a national status in some countries while in others they are confined to the single institutions responsible for the clinical trials. In some cases a hierarchy of responsibility and authority is established ranging from institutional ethics committees through professional councils or colleges to national authorities. In many cases, moral authority is considered more effective than legal obligations.

This wide range of approaches is exemplified by the situation in the United Kingdom and in France. In the former country the ethical review process is carried out since 1967 by as many as 200 different Ethics Committees, mainly based within single institutions, while in the latter a permanent National Advisory Committee was established in 1983, endowed with the responsibility of giving effective and authoritative statements on different issues.

A process for harmonizing national authorization procedures is being developed at the European level through the concomitant activity of different organisms. The Commission of the European Communities has been particularly active in developing common protocols for the authorization of new drugs and has progressively established scientific criteria for the evaluation of medicines for human use to be recognised by the 12 Member States.

What the standards are set for

The need to fully respect the human individual, while allowing scientific and technological developments on which not only the progress of knowledge, but also the health and even the survival of a large number of people depend, poses profound ethical dilemmas. Continuous intellectual efforts, as well as moral commitment, are needed to solve such dilemmas. Standards are set to guide the individual physician or biomedical scientist, research teams, institutions and the authorities, in establishing which goals are desirable, acceptable, legitimate and which means may be used in the pursuit of such goals and under which conditions.

From pre-conception to death, the whole life span of man is made the object of biomedical research. The study of gametes, in vitro fertilization, research on embryos and fetuses, organ transplants, artificial organs, survival in coma, radical and imaginative surgery, trials of new drugs affecting even the very essence of the individual, namely his way of thinking and feeling, ever more revealing but sometimes dangerous diagnostic procedures, all these biomedical actions on humans require terms of reference and guidelines of conduct, so that the individual is protected, yet progress is not hampered. That is what standards are for. The most important general and specific issues on standards will be dealt with in the course of this meeting.

Two previous "Summit Bioethical Conferences" discussed in depth the problems related with research on the human genome and embryo (Rambouillet 1985), and with neurobiology (Jakobsberg 1986).

Among the different issues concerning research with human subjects, those related to clinical trials of new drugs deserve particular attention because of their very wide economic and industrial, as well as medical and social, implications.

The 1983 CIOMS document suggests that some simplification of procedures and flexibility is desirable in the early clinical trial phase. However, procedures are to be established in order to evaluate new substances in an efficient and safe way by means of preclinical examination on animals and subsequent experimentation on man up to the point where therapeutic activity is demonstrated and the toxicology defined. The balance between risks and benefits, to be dealt with later today, is of paramount importance.

All previous information and knowledge must be utilized with great care and all experimentation on man must come after precisely targeted preclinical research. Furthermore, an increasing role should be given to clinical relevant essays carried out on in vitro systems which are now being provided by modern biotechnology. In particular, the possibilities offered by human cells cultures in vitro should be fully exploited.

The methods of monitoring the response to drugs and the criteria for the selection of the subjects to be studied should be carefully established. Furthermore, each clinical research project should be examined by an independent Ethical Commission and be supplemented with written protocols defining the objectives, the methods of analysis and the safety requirements. For industrially relevant research, confidentiality concerning the product, and transparency of the financial arrangements and interests should also be considered.

The situation existing in different countries is summarized in Table 3. A preliminary authorization before starting clinical research is formally requested in some countries (for instance Italy, the Netherlands and Spain) whereas in some others (notably France and the Federal Republic of Germany) it is substituted by a simple preliminary notification to the competent authorities. Finally, in some countries, e.g. Switzerland, neither notification nor authorization are necessary.

Concerning the problem of consent, a distinction between therapeutic and non-therapeutic research is to be made, as suggested by the Helsinki/Tokyo Declarations. Specific requirements should be satisfied which generally imply that the patient is completely free to give his approval and decide to withdraw it at any time during the experimentation. He must be duly informed about the objectives of the research and the inherent methodologies and be aware of the possible risks and benefits of the proposed trials.

In case of legal disability of the research subject, consent should be obtained from its legal representative, and, in case of physical disability, the legal representative's consent will substitute that of the patient.

The guidelines published in 1978 by the Food and Drug Administration in the USA specify that a written consent is required in clinical research at phases 1 and 2, corresponding respectively to the assays on healthy volunteers and early clinical trials, whereas at the subsequent phase 3, involving large scale experimentation, the physician is entitled to establish whether the consent is given in written or verbal form.

Priority must also be given to the independence of the researcher, with the understanding that his responsibilities cannot be transferred to the volunteer or to the patient.

The assessment of the benefits and disadvantages to be expected from new products should be pursued well beyond pre-registration clinical trials and be continued during the stage where the new drugs are allowed on the market and used by the population at large. In fact, "pharmacovigilance" is now considered an essential tool for evaluating the real practical value of a product, and for identifying long-term and/or rare effects which may have escaped pre-registration studies.

Current clinical research requires experimentation on a blind or a double-blind basis. In the first case the patient is not aware of the nature of the treatment he receives, while in the second case neither the patient nor the doctor know whether the medicine is a new drug to be tested, the reference product or just a placebo. It is evident that in such cases the requirement of scientific objectivity prevent complete information of research subject.

A similar problem is posed by the related case of randomized testing. Here patients are randomly distributed among different groups receiving alternative treatments. Should the patient be informed about this procedure? Is it ethically acceptable to deny a certain number of patients the best possible known treatment? It must be kept in mind that the patient's interest should come first and that he must always be treated according to a safe therapeutical protocol.

This is especially true with particular groups of human subjects, such as expectant women, children and aged people, prisoners, coma-patients and, in general, human beings not having a normal mental and/or legal capacity.

Rules have been established that no experimentation should be carried out on these cases and that exceptions are only allowed in emergency situations or in order to obtain a direct and clear health benefit.

The problem of the therapy of mentally-ill persons was examined in the previous Summit Bioethics Conference held in Jakobsberg (Germany) in 1986. It was suggested that in the case of patients "whose ability to factually understand and consent to treatment are limited or absent, a third party permission (proxy consent) is indispensable and should respect the principle that the benefits outweigh the risks".

A particular problem is posed by the use of human biological material for diagnostic and therapeutic purposes. Cultured human cell lines and hybridomas have been developed for therapy and research, raising problems similar to those encountered in organ donation and transplantation. It would be important to further discuss this issue in order to develop proper regulatory principles.

How the standards are set

Different systems are operating in the process of standard setting. As we have seen earlier, very many Ethics Committees have been set up to issue guidelines or rules and to define procedures. This complex and diversified process is preceded and accompanied by a debate pervading society at different levels. Acceptable standards should reflect public consensus. Eventually, such a consensus should be attained by confronting the points of view of the different components of society and by integrating the opinions of scientists and medical professionals with those of lawyers, jurists, philosophers, moralists, theologians, as well as social experts, economists and industrialists. This conference certainly reflects this trend since it brings together experts of a very diverse background and promotes a multi-faceted discussion of the problem.

Research on embryos and foetuses is the subject of passionate multidisciplinary discussions. On this issue, the basic philosophical and religious premises are still so different, even within the relatively homogeneous countries which are members of the European Community or the US and Canada, that consensus seems far. Discussions, debates, and efforts of mutual understanding must be pursued if common standards are finally to be adopted. Though less immediately exciting for the general public, the problem of human experimentation of new drugs and of the "pharmacovigilance" of registered ones is possibly of even greater relevance for the future of human health and/or the economic viability and fair competitiveness of the pharmaceutical industry. Industrialists should therefore be also consulted in the preparation of standards, and held responsible for their respect.

As an example of a multinational, intergovernmental, standardization process, one could mention the effort carried out within the Council of Europe and the European Community to harmonize national authorization procedures for the evaluation of human medicines (see Table 4).

One major goal is that the analytical and pharmacotoxicological tests as well as the clinical trials of drugs carried out in one Member State in accordance with Community rules need no longer be repeated within the European Community in order to obtain authorization in other Member States. The registration of medicinal products should thus be facilitated and duplication avoided. Within the EEC the authorization to commercialize a medical substance is established through a "multi-state" procedure as envisaged in Directives 75/318 and 83/570. Concerning clinical trials it is especially required that toxicological and pharmacological assays on animals must always precede the therapeutic experimental phase on man. The pharmacological data should include possible modifications of the response to the drug following prolonged use as well as secondary effects occurring when it is combined with other drugs. Clinical data and general conclusions must be transmitted to competent authorities. The clinician must exert particular attention to addiction problems presented by a new drug or by detrimental effects of its association with other components.

In 1985, a Directive was adopted concerning the registration of pharmaceutical products obtained by biotechnology.

By adopting Directives 83/570 and (quite recently) 87/22, the EEC is in the position to choose, before 1992, the definitive system of the free movement of medicines within Member States.

Furthermore the Commission of the European Communities has recently transmitted to the Council of Member States a proposal for a directive concerning transparency in the national systems for controlling the prices of medicinal products and their reimbursement by social security. This policy undoubtedly has an important ethical contact, since it is aimed at preventing undue speculation on human health.

Of particular value in the bioethical context of human experimentation is the "European Guide of Medical Ethics", recently issued by the International Conference of the European Medical Orders (Paris, January 1987). The Guide is composed of 38 articles covering the whole problem of the professional conduct of physicians in their relationships with patients, society and colleagues. It recommends that the Medical Orders of each Member State of the EEC take the necessary provisions to comply with the principles announced in the Guide.

The Council of Europe has also been recently charged with the task of defining rules concerning medical research on man.

Future developments and actions

An analysis of the present international and national situation indicates that, although the regulations adopted and implemented by different industrialized countries are far from being harmonized and the existing provisions are not always optimal, the system in use is essentially valid. This is not always the case in some developing countries which are often lacking proper tools and have insufficient regulations. Such countries run the risk to be chosen for the performance of human experiments of doubtful significance or of considerable danger.

Agreements should be sought about "minimal" standards for experimentation on humans to be adopted by all countries. Moreover, it could be established that human experimentation should not be carried out in a country, unless it is aimed at treating a pathological condition which is important to that country.

International fora, such as those organised in the frame of economic Summits can provide an authoritative support to the discussion and solution of all these problems.

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TABLE 1
INTERNATIONAL DECLARATIONS AND GUIDELINES

	Affirmed Principles
Nuremberg Code (1947)	Voluntary consent; researcher responsibilities; previous experimentation on animals; study assessment; avoiding suffering and risks; avoiding lethal or disabling experiments; evaluating risks and benefits; qualified scientists as researchers; terminating experiments on a voluntary basis both by subjects and by researchers.
Helsinki Declaration (1964)	(Adopted by the World Medical Association and modified by the World Medical Assembly in Tokyo in 1975). Full responsibility of researcher; risk-benefit ratio to the advantage of the patient; priority of patient interests; obligation to obtain a free and informed consent from the patient.
CIOMS (Council for International Organisations of Medical Science) and WHO (World Health Organisations)	"Proposed International Guidelines for Biomedical Research involving Human Subjects" (1982) "Safety Requirements for the First Use of New Drugs and Diagnostic Agents in Man" (1983) Defining safety standards in preclinical stage, before early clinical trials. Objectives of early human studies: - probing a useful pharmacological action on man; - defining the drug concentration in relation to individual variability and safety limits; - developing dosage tables to be used in subsequent clinical evaluation; - developing methods to minitor individual and objective response; - selection of subjects to be based on the type of drug to be evaluated more than on a general procedure; - protocol examined by independent Ethical Committee.

TABLE 2
WHO SETS THE STANDARDS AT NATIONAL LEVEL

Austrilia	Australian Drug Evaluation Committee Ethics Review Committee of Hosting Institute.
Austria	Federal legislation of 1983.
Belgium	Code of Medical Ethics prepared by National Order in 1975. National Ethical Committee at Medical Research Fund.
Canada	Food and Drug Regulation, Bureau of Human Prescription Drugs.
Denmark	Legislation of 1975. Notification to National Health Service.
Finland	Guidelines of National Board of Health in 1980.
France	Notification to Ministry of Health. Good clinical trials practice of Ministry of Health. A "Comité Consultatif National d'Ethique" was created in 1983.
Germany	Notification to Federal Bureau of Health (BGA). Ethical committees at regional or local level.
Greece	Guidelines in 1984. Notification to National Bureau of Drugs.
India	Guidelines on Introduction of New Drugs by the Central Drug Standard Control Organisation in 1985. Ethical Committee of hosting Institutions.
Italy	Legislative provisions in 1973 and 1977. Committee for the Evaluation of Requirements for New Drugs at the National Health Institute (ISS).
Netherlands	Guidelines of National Health Council of 1955 and of Medical Research National Fund of 1979.
Norway	Legislation in 1978. National Centre of Medicinal Products Control.
Spain	Legislation in 1978. Ethical committees referring to Helsinki Declaration and National Medical Order.
Sweden	Compulsory notification to National Board of Health and Welfare.

Switzerland	Guidelines from National Academy of Medical Sciences in 1970 and 1981. Ethical committees.
United Kingdom	Investigational New Drug Provisions, IND, of Food and Cosmetic Act of 1962. Authorisation from FDA. Good Manufacturing Practice (GMP).

TABLE 3

SUMMARY OF PROVISIONS ADOPTED BY DIFFERENT COUNTRIES IN RELATION TO CLINICAL TRIALS

	Preventive authorisation	Ethical Commission	Legislation	Guidelines	Informed consent
Australia	+	+	+		+
Austria			+		
Belgium		+		+	+
Canada	+	+	+		+
Denmark			+		
Finland		+		+	+
France	+				
Germany W.(FRG)		+		+	+
Greece			+		+
India		+		+	+
Italy	+				
Netherlands	+	+		+	+
Norway		+	+	+	
Spain	+	+	+		+
Sweden		+		+	+
Switzerland	+	+	+		+
United Kingdom	+	+		+	+
USA	+	+			+

TABLE 4

HOW THE STANDARDS ARE SET AT EUROPEAN LEVEL

European Community (EEC)	Common scientific criteria for the evaluation of human medicines and harmonization of the national authorization procedure have been established by means of several Directives and two Council Recommendations. The tests and the trials carried out to obtain authorization do not need to be repeated within the EEC. Cooperation between the 12 Member States and the Commission of the European Communities was fostered by the Committee for Proprietary Medical Products. A multi-state procedure, effective in 1986, has replaced this committee.
Nordic Council on Medicines	Instituted in 1975 by Denmark, Norway, Sweden, Finland and Iceland. Specific guidelines for clinical trials have been established: the study should be conducted on healthy volunteers; the new drug is evaluated in relation to the pharmacological category to which it belongs.
Comecon	The Sanitary Commission of the Mutual Assistance Council includes the East European countries, Cuba, Mongolia and Vietnam. Guidelines for the verification, assessment and standardization of medicinal products were established.
International Conference of European Medical Orders	The International Conference of Orders and similar organisms held in Paris in January 1987 has issued a "European Guide of Medical Ethics" containing the principles aimed at inspiring the professional behaviour of doctors. The guide analyzes the problems of pledging, of informed consent, of moral and technical independence, of professional secrecy, of competence, transplantation, reproduction, experimentation on man and other issues.
Council of Europe	A preliminary list of principles concerning medical research on man has been drafted.
European Association of Centres of Medical Ethics	Preparing a comparative study on different Medical Ethical Committes operating in Europe.

DISCUSSION: Liborio Falanga

Thank you very much Mr. Chairman. The rich report given by Mr. Fasella extends the consideration of ethical problems beyond the problems of relationships between doctors, researchers and patients, and into general economic relationships concerning the health industry. The European Economic Community, for example, can impose directives on its twelve states on the basis of the free circulation of goods, including drugs. This requirement of free movement imposes a common method for control. We should ask ourselves if this regulation truly incorporates the ethical position of the Community or of the states which are part of the Community.

This leads me to make a few theoretical comments concerning the choice of authority to establish the standards, the levels at which we can establish responsibility and decision and the degree to which to seek solutions acceptable at the international level.

My comments are intended to give a few general ideas to help us to find common guidelines for problems raised in biomedical research.

The growing interest of the modern world in the development of scientific research aimed to improve the health of man has given rise to questions concerning the lawfulness of experimental research which is in conflict with human rights, as well as the acceptability of some systems and techniques which go beyond the human dimension and may replace human functions.

The idea that these problems cannot be resolved by individual states, but require an international agreement for understanding which takes account of the international value and the applications of the research in this area, leads us to think about the validity of recent international documents. We need to examine their level of acceptability and their relative flexibility, as well as their ability to be translated into legal norms or regulations which state legislations can impose, with clear sanctions where the rules are not respected.

The Latin legal system which characterizes the laws of the Mediterranean states is founded on Roman law. It seems very timely in this meeting to recall some of the Roman principles, such as the assumption that the legal norm does not precede but rather strengthens and guarantees de facto situations, thus, giving certainty to interpersonal relations between subjects and community, between citizens and structures which are organized by the state. It also gives importance to the value of the legal norm which is imposed by the system. The strength of the norm is drawn from the severity of the sanction. The more severe the sanction, the more important is the interest to be protected by the violated standard. In any development of a legal standard to govern the behaviour of subjects, the protected value is important. It may be political, social or national or ethical.

When a value is confirmed in declarations of international law, the states find it easy to implement, given the common feeling of the international community on a specific problem, aspect or behaviour. If this were true, we would have already had in the international community, as well as in national legislation, guidelines and principles which would be translated into law. This has not yet happened. This meeting shows the necessity of finding international agreements which are closer to the common feeling of the national communities.

This is neither simple nor easy for two reasons. The first is based on the way we develop international agreements. Restrictive work groups, almost always made up of experts where it is easier to reach an agreement due to the fact that everyone speaks the same language, pursues the same goals, and operates in the same way, develop guidelines on a technical level. These are then handled by other experts with more wide spread interests which often are in conflict with the technical assumptions of the researchers. The international scientific community is thus forced to identify different values, procedures, and guidelines which can resolve conflicts between the social needs, which is normally the aim of research, and the individual rights of subjects who as citizens hold personal subjective rights which are sacred according to the constitution of their own state. It is clear that the progress and the freedom of scientific research cannot be anchored in static principles. Bioethics aims to analyze and identify the boundaries within which research justified both in the ends and the means can operate.

Beyond this, the rational supremacy of the rights of man which has already been established in international declarations that we have seen in Miss Miller's report limits the expansion of research to fairly well-defined assumptions which have some practical application. On this point we should ask ourselves if it is better to identify values or if we should establish the boundaries of research. The first assumption is preferred by researchers, but when we think about it in such delicate sectors as experimental research on the very essence of man, we are left with a feeling of discomfort. Even if the research aims to cure and prevent genetic or degenerative diseases, the freely consenting subject may experience considerable risk. So far, the regulations which we find in international documents have not left sufficient room for the diversity of different countries concerned. As a result, it is possible to envisage in the legal systems of different states, these different international agreements. If we look at the reality of the seven countries which are present here, we could act backwards. We could have an analytical comparison of the internal fundamental guidelines within which we can reach an agreement. The results would be more positive.

The idea of setting up an international institute of bioethics as a centre of study and research for an international association could be favourably received. The Italian government would favour this. The analysis of the fundamental guidelines of the states which are present here should be examined to see if research on human subjects is lawful or not. From the Italian point of view, what counts at the present time is asserting that in developing standards and guidelines in this area, the authority exists at different levels as a series of regulations. The framework laws are set by the national Parliament and lead to regulations and procedures at the level of the government down to practical regulations which apply to specific sectors.

At the international level, while awaiting the provisions concerning the physical integrity and the human dignity of people, as was pointed out by Dr. Fasella, the Council of Europe, proposed that valid ethical principles for every relationship between subject and researcher should respect certain ethical codes, which should be self-policed by a professional association.

This assumption is not very convincing because the system would not impose sanctions other than mere disciplinary sanctions. Doctors and biologists cannot impose legal sanctions, for example. Others feel that in the health sector the declaration by an independent ethical committee would give a better assessment of the legitimacy of the consent of the individual or of the validity intervention of the physician and would guarantee the basic rights of life and health of the subjects involved in the research. In Italy the fear that the doctor passes onto the Ethical Committee his choices of professional responsibility, choices which can be assessed only by those who are experts in that field of medicine, is not compatible with an independent ethics committee.

The problem that the legislator must face is that of having to involve himself in the details of medical intervention. This leads to further problems when we get into the very specific regulations concerning intensive therapy, organ transplants, as well as other aspects.

With respect to the presentation given by Dr. Fasella, we should assess to what degree we can establish directions and procedures to go beyond opportunities which the individual states have in respect to common requirements and common feelings which can be translated into ethical norms. Eventually if we want to arrive at a more legislative standard, sanctions which guarantee at every level, respect for the dignity of life as well as the dignity of the human subject should be delivered through professional sanctions with respect to the physician, researcher, or other individual who violated the ethical standards.

Document 4

THE ROLE OF THE PUBLIC
LE ROLE DU PUBLIC

Gordon R. Dunstan

Discussion: Abbyann Lynch

Session D / Séance D

International Summit Conference on Bioethics
Colloque international de bioéthique

The Role of the Public

PRESENTATION: Gordon R. Dunstan

Introduction

The public is involved in research with human beings in four ways. It stands as a potential beneficiary. It risks being a victim. It has influence as a determinant of policy. It is increasingly a participant in decision. For the avoidance of overlap with another paper (Sir Raymond Hoffenberg's) this paper will lead only to the threshold of the fourth activity, participation. As for the first three, the author is aware that his reflections stand on little documented research, but on personal speculation. They are offered therefore with diffidence.

The Public as Potential Beneficiary

Observation and deduction, within the overall philosophy of ends and permitted means, have always stood at the heart of good medicine. The benefit was related to, and therefore limited by, the knowledge available in each epoch; and knowledge was limited by available technology and skill. The advance from observation and empirical trial to planned investigation and controlled trial, which underlie contemporary medical research, coinciding with advances in technology and knowledge in other branches of science, has undoubtedly brought extensive benefits in the control of epidemic disease, the promotion of preventive medicine and the clinical treatment of individual patients. Further research is undoubtedly a condition, though not the only condition, of further benefit. As William Harvey remarked three and a half centuries ago, commenting on a statement of Galen that "the treatment of a patient was merely the matter of applying the remedies known to be effective for certain symptoms", *Quomodo, nisi experimentum*? "*How* do you know, without the proof of trial?" (Keynes, 1966)

This reliance on research as a condition of benefit is accepted as axiomatic in the Declarations and Codes designed to regulate practice, whether in research with animals or with human subjects, consistently with accepted ethics and to minimize abuse and hurt. It is common practice, for instance, in the United Kingdom, for a copy of the Declaration of Helsinki, as revised in Venice in 1983, to be annexed to protocols for clinical trials of new medicines, and investigators are expected to comply with its requirements. Local Codes, like those of the Association of the British Pharmaceutical Industry, (ABPI), add precision with the intent of safeguarding the respective interests of manufacturers, practitioners and research subjects or patients in the conduct of trials. It is acknowledged, therefore, that the public which is a potential beneficiary of medical research has also interests to be defended. There is no benefit in medicine without attendant risk; and, the more potent the remedy, the higher must be the risk of contingent or collateral harm.

The Public as Potential Victim

"The public" is, of course, an abstraction. It consists of a society of persons and corporate groups, natural and conventional. But it is not a mere aggregate of individuals and units; it has a corporate interest of its own. "The public" today is well aware of harm which may come to it from medical research; and sometimes it would seem to articulate that awareness more loudly than its acknowledgement of past and potential benefit. Experimental subjects may be harmed in the experiment, by direct or side effect - and tools for assessing the risk of harm, to be set against sought-for benefit, are being fashioned and put into use (Nicholson, 1986). The harm may not be physical or psychological only. People are as sensitive now to assaults upon their liberties as they are to bodily hurt. Research conducted without the knowledge of its subjects (as, to take a topical examples, in proposed schemes for screening for AIDS), or without information adequate for the giving of true consent, is taken as an assault upon human liberty. Research procedures upon infants without the knowledge and consent of parents are not the more acceptable when excused by, for instance, the need for the investigation to be made soon after birth, or the possibility that the child itself *might* benefit from the study, even though it is directed primarily at the gaining of beneficial knowledge. Such short-term expedients by researchers undermine trust, and trust is a precious bond in society, especially in the practice of medicine. There must be a presumption in every medical treatment that it is for the patient's good. A procedure which falls outside that presumption, however estimable its purpose in the pursuit of knowledge beneficial to future practice, unless it is presented to the patient as such, must weaken faith in the presumption, and so lessen the trust on which the relation between physician and patient stands. If fairly presented in such a way as to win consent and co-operation, the research project and the common good stand to gain.

There are other areas of research in which the public feels threatened, each by an extension of emotional identity. The first is with human pre-embryos, in the context of fertilization *in vitro*. The second is with animals. Feeling extends from unease and inchoate concern at one end to a sometimes pathological anger, bursting out into lawlessness and violence, at the other. The language of rights is employed as though it were the only means to afford protection: both the pre-embryo and the non-human animal are invested with rights, when in fact neither is a bearer of rights known to the law. It is commonly forgotten that even where there are no rights, duties can be owed. To the embryo and to the animal we owe duties, enforceable by law. There are wide and legitimate differences of opinion about when the duty to protect the human embryo begins, and on whether the interests of medical research are strong enough to rebut the presumption in the embryo's favour.

Equally wide are the differences about the use of animals in medical research. Some extremists would outlaw it altogether, denying both its permissibility and the fact or prospect of valid benefit from it. Others regard it as a regrettable necessity until valid alternatives can (if ever) be found. Still more, while allowing it for genuine medical research and tolerating it when required by statutory safety regulations, would refuse it absolutely for "non-essentials" like cosmetics (which are commonly assumed to be in a narrower range of products than in the new European Economic Community definition), food colourings and the like. All are agreed that the purpose must be serious; that the potential benefit must be real; that the suffering inflicted on the animal be not disproportionate to the potential benefit; and that the suffering be kept to a minimum and eliminated altogether when that can be done. Parliament has recently enacted of a new Statute, the Animals (Scientific Procedures) Act 1986, to reinforce these principles. Parliament has also before it the proposals of the Warnock Committee to regulate the experimental observation and use of human pre-embryos by a similar enactment embodying similar procedures (Warnock, 1984). Meanwhile, public interest is high, and feelings are easily aroused to influence the shape of public policy.

The Public as a Determinant of Policy

It is proper to a liberal society that its people should not only be able to contribute to public policy but also that they should be educated and equipped to do so. At the highest and most formal level, public influence is exerted through Members of Parliament in legislation and through juries in the trial of actions and prosecutions in the Courts. It is probably fair to say that, in matters concerning research, juries are better instructed that Members of Parliament, Juries are instructed by the judges. MPs are swayed by pressure groups and by covert and overt lobbying. Public attitudes are formed very much by media of communication, notably now by television. And since adversarial procedures make what producers call good television, issues are often polarized by the bringing together of extremists and members of pressure groups to argue their case. Inevitably emotions are roused; and only sometimes can it be surmised that the viewing public has emerged better educated by the experience and better equipped to urge an informed opinion and will as a contribution to public policy. It requires but one flagrant breach of the rules, whether deliberate or inadvertent, by a researcher with animals to arouse a tide of protest against the whole system. Similarly, it requires but one bizarre outcome of treatment for infertility - a high multiple pregnancy, perhaps, from miscalculated hormone adminstration of from cavalier replacement of embryos fertilized in vitro - to rouse hostility to all experimental embryology to well-reasoned proposals for its continuance under regulation.

Members of Parliament are powerfully swayed by these surges of emotion. Recent Private Members Bills designed to halt all experimental use of human pre-embryos, for which the arguments were seldom grounded in an awareness of the facts or a sound grasp of the relevant principles, were halted in their progress towards the statute book only by the responsible manipulation of Parliamentary procedures. The standard of debate on the Warnock Report, in both Houses of Parliament, was, on any rational reckoning, low.

It is tempting, therefore, to be either cynical or despairing about the public contribution to public policy, especially when scientists in other liberal societies are being denied the professional freedom still enjoyed, though threatened, at home. There are grounds on which to believe, however, that given time, rationality, that essential ingredient in morality public as well as private, will prevail; and that it will result, either in a good stature from Parliament, or in reliable judgments from the Courts. Despite the polarized propaganda over research with animals, Parliament has enacted, after years of careful preparation in the Home Office and of responsible debates in both Houses, a new statute which all parties, except the most extreme, believe to be well wrought and capable of fair trial. Therein lies ground for hope that, given time and constructive education, progress in medical research with embryos may be maintained under proper control.

Where opinion has been carefully tested, results indicate a weight of hitherto inarticulate opinion sufficient to invalidate the claims of anti-research pressure groups to represent the only tenable opinion on the matter - successful though they have been in mobilizing MPs.A study was made of the attitudes of women or reproductive age in Edinburgh to in vitro fertilization and embryo research (Alder et al, 1986). A questionnaire was given to 1920 consecutive women attending clinics for family planning, ante-natal care and infertility. The response rate was very high, ranging from 79% in the ante-natal group to 96% in the family planning group. Overall, 94% wee in favour of IVF treatment; 67% approved of research on human embryos up to fourteen days to improve IVF treatment, and a further 10% (that is 77% in all) supported research on embryos designed to avoid birth defects. A majority, 70%, thought that women should be allowed to donate ova for research. In the social analysis of the groups, neither age nor social class was related to attitudes to embryo research. Religion was. In the ante-natal group and the family planning group, Protestants were the more favourable towards research. In the ante-natal group, Protestants were more willing to donate ova for research than were roman Catholics. But in the family planning group, 65% of 92 Roman Catholics were pro-research and 55% were willing to donate ova for it. The religious variable was more powerful than age, parity or social class, and may have played an important role in forming public opinion.

The survey illustrates what can be done to estimate public attitudes by careful means taken in suitable contexts. The groups had a relationship of interest with the research, related to the service sought: an interest which showed them that research could be purposive and not an arbitrary pursuit. They were given time to inform themselves and to consider their replies: the forms were completed in the waiting-rooms of the clinics. Serious attempts to inform the public on issues involving research in ethically sensitive areas are well received. A Report published by the Council for Science and Society entitled Human Procreation: Ethical Aspects of the New Techniques (CSS, 1984) is said by its sponsors to be the most widely read of all the Council's Reports and by its publishers to be a commercial success. The Board for Social Responsibility of the General Synod of the Church of England published a Report on human fertilization and embryology in order to inform Christian opinion on the elementary facts and the ethical issues at stake (BSR, 1985). Two and a half years after the publication of the Warnock Report the British Government has issued a consultation paper (DHSS, 1986) setting out the options for legislation on infertility services and embryo research and inviting comment from interested groups and individuals. In Australia also, where research in this field is advanced and is the centre of controversy, the National Health and Medical Research Council performs a similar deliberative and informative task (NHMRC, 1983).

The eventual enactment of the Animals (Scientific Procedures) Act 1986 owed much to the careful education of public and parliamentary opinion by middle-ground bodies like the

Universities Federation for Animal Welfare (UFAW), the Fund for the Replacement of Animals in Medical Experiments (FRAME), and the Committee for the Reform of Animal Experimentation (CRAE). The Institute of Medical Ethics in London, which combines research and publication in medical ethics with education in medical schools, has recently obtained substantial funding for a study of the use of animals in medical research with a view to promoting informed public discussion based on a non-partisan presentation of the relevant facts within the necessary structure for ethical analysis (IME, 1986, 1987).

Public Participation

Public participation goes further than mere discussion, lobbying and the exertion of political pressure. There are areas of medical research which rely on volunteers to take part in studies and trials. Healthy volunteers are required as well as patients, depending on the nature of the research. Comparative studies of new medicines in general practice require the co-operation of patients, sometimes over a long period. The trial of vitamin supplements for the prevention of spina bifida in high-risk pregnancy requires participants of a high moral courage: for once it has become known that supplements may have lowered the incidence of fetal deformity there is a strong emotional dissuasive from accepting the possible loss of benefit inherent in the placebo. If the ranges of the normal, in infants for instance, need to be studied as indicators for the pathological, mothers and fathers have to be persuaded to allow the inclusion of their infants in the study. The respective duties attending so-called "therapeutic" and "non-therapeutic" research are set out in the Declarations and guidelines; but success in research of both sort requires consent and commitment from patients and human subjects - from members of the public.

Public participation is now carried further, into the actual supervision of medical research itself, through lay membership of what are called in Britain Research Ethics Committees and, elsewhere, Institutional Review Boards. Definitive guidelines for the constitution and working of such ethics committees were issued by the Royal College of Physicians in 1984 (RCP, 1984). They operate in District General Hospitals, Universities and Medical Schools, and in registered private institutions where developmental infertility services are offered and attendant embryo research is done. The Voluntary Licensing Authority, established jointly by the Medical Research Council (MRC) and the Royal College of Obstetricians and Gynaecologists (RCOG) to supervise IVF and embryo research until a statutory body is set up, has a lay chairman and six other lay members who participate fully with the eight practitioners in clinical medicine and research (VLA, 1986). The Royal College of General Practitioners has nursing and lay members on its Clinical Trials Ethics Committee.

Lay participation in Research Ethics Committees, if it is to be effective, is demanding. The first requirement of a research proposal is that it be well designed, grounded in good science, directed towards a good end, and so designed as to be able to meet that end, to give answers to the questions raised. Few lay members have sufficient knowledge either in the relevant science or in the statistical and other skills required to judge whether the design is good or not. Without the assurance that it is, they cannot pronounce upon the ethics. It is necessary, therefore, first that the Committee has available to it an assurance from someone competent that the design is sound (or reasons for saying that it is not); and secondly that there be such rapport in the committee that lay questions can be asked, considered and answered. In good practice the chairman would invite elucidation of facts and empirical features - e.g., the nature of the intervention, the seriousness of sequelae and risk - before consideration of merits. Lay members owe it to their colleagues also not to rely only on emotional reaction to a proposal, but to school themselves in the art of moral reasoning and analysis. The work or Research Ethics Committees, new as it is, is under regular review, formally in conference at the invitation of the Royal College of Physicians independently by voluntary bodies committed to good medicine and to the public interest alike (Nicholson, 1986; IME Supplement 1986).

Conclusion

The second half of the twentieth century has seen advances in medical science and technology more extensive, perhaps, than ever before; and may well see more. these have brought great benefits. They are seen also as threats: power is always reared. At the same time have come changes in the public attitude to medicine. While most patients go on quietly trusting their doctors and most doctors quietly advise their patients, titrating the information given, so to speak, according to the patient's capacity to receive, the public voice tends to proclaim an end to "paternalism" and a new era of "autonomy". In this context the defence of patients and research subjects can take aggressive forms. Philosophers creating a new academic subject and structure called medical ethics stretch the language of rights, and lawyers put it to litigious use. An adversarial relationship is cultivated in the public mind in place of one of partnership and trust. The parties are polarized into deliverers and consumers of health care. Medical research is at risk in such an atmosphere.

The change of attitude has gone less far in Britain than it has elsewhere. We have a tradition of professional self-government within statutory limits; our conduct is governed more by convention than by fear of the law. There is still time to bring the new generation of research within the same sort of control. The immediate task is, by education and steady reasoning, to win commitment in the middle ground.

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DISCUSSION: Abbyann Lynch

Thank you, Mr. Chairman. We are indebted to Professor Dunstan for his lucid analysis of the public's role in research, particularly for his contribution of helpful examples illustrating this role as arising from the United Kingdom experience.

To build on Professor Dunstan's comments and to recast them slightly, I suggest two lines of thought for further discussion.

Number One. Professor Dunstan spoke of the public as beneficiary in terms of research. He spoke of the public as potential victim of research. I should like to make mention also of the public as harmed by research which is not done.

In a sense, this point is made as continuation of his discussion concerning the pre-embryo research debate. The difficulty is more extensive than that raised in his comments, however. Much other research which appears needed is not being done. There are various reasons for this: as in the case of the pre-embryo, for example, because of deference to the public's moral view of what is fitting or right.

In this matter, there is a concern in Canada around the use of incompetent research subjects-children and other individuals who may be cognitively impaired, such as victims of Alzheimer's disease. The concern is that the fiduciary relationship existing between these individuals and their parents/guardians not be fractured as those parents/guardians allow such incompetent individuals to be used for purposes not directly beneficial to them. In the past, those groups not benefitting from research which was scientifically possible but not pursued because of ethical concern, were identified as therapeutic orphans.

The serious ethical problem here is to identify which groups would really be harmed if certain research were done and which would be harmed if such research were not done. At the level of public policy, one can point to several examples of research not done, both within and beyond Canada. The proponents of the research in question might well claim that harm was perpetrated or benefit not forthcoming as a result of non-activity here. The debate surrounding the recombinant DNA research moratorium comes to mind as does the present debate regarding somatic and germ-line gene therapy.

In this matter of non-benefit or harm arising from non-research, the role of the public as non-beneficiary or potential victim is of great importance. So also is its role as policy maker generally and as decision maker at the level of Research Ethics Boards or institutional review boards. The charge that non-research engenders therapeutic orphans is a serious one; it may well be legitimate.

Less problematic is the concern that research for which there is serious local or national need is not pursued, on the ground that the outcome of such research will not be commercially attractive. In this conference, which is specifically concerned with research interdependence in the world, I refer particularly to the research needs of developing countries. The concern regarding non-pursuit of commercially non-attractive research in such areas has little to do with concern for harm to potential research subjects. Rather such research is not pursued by the jurisdictions concerned because they lack the research capability to do so; it is not pursued by other groups since it might not be profitable to do so. The work of the World Health Organization in this regard is to be recognized as a model for those concerned about research ethics in this interdependent world; some such ongoing effort to engage in and to encourage research needed by those groups unable to pursue it on their own is much needed. Stated differently: is there not an ethical obligation to pursue certain research, despite its commercial unattractiveness, even as there is an obligation to ensure that any research pursued is pursued in an ethical manner?

As a first point then, non-research can be harmful to the public. Such a stance may deprive certain groups of benefits and it may also harm them. Discerning the difference between non-research of this kind and non-research as prevention of harm, as conferring benefit in its absence, is part of the public's task, as outlined by Professor Dunstan. In its several roles related to policy and decision making, the public must advance ethically acceptable research even as it must require, on ethical grounds, that certain research be done. As a group, this conference should address the question of non-research, giving some direction to the discussion regarding the two areas mentioned. It should concern itself with therapeutic orphans: those created by non-research on grounds of public morality and those created by non-research on grounds of commercially non-attractive outcome.

Number Two. Professor Dunstan came close to addressing the question of public in its role as supervising research by way of membership in Research Ethics Committees at universities, hospitals, and the like. This particular role is well-developed in Canada and the United States but it is still evolving. To speak to the Canadian experience particularly and as paradigm for some other jurisdictions, the revised Medical Research Council Guidelines you have all received identify the Research Ethics Committees as representing "the values of the particular community", these values being the matrix of ethics review.

Presumably, that same concept would apply to research ethics review groups, whatever their location. It is this particularity, this deference to local mores, which is not without difficulty in the national or the transnational perspective, however fitting it may be at the local level. To speak to one of Professor Dunstan's concerns, for example, the Canadian document notes that, as regards pre-embryo research, "research proposals will vary with regional and individual differences". The implications of locally-based autonomy regarding the values which are to guide approval or rejection of locally conducted research are profound as regards consideration of multi-centred and possibly international research, whether in terms of pre-embryo research or other experimentation.

In providing guidance on this point, the Canadian Medical Research Council advises that "no pressure should be applied or permitted which reduces institutional autonomy or comprises its sense of propriety". Specifically rejected is a single national position regarding research ethics, except as may occur by way of law. Such a stance, in this case a Canadian stance, may well be at odds with that of other countries where research ethics policy is determined centrally.

Further, in ethical terms, this principle of local accountablity and local responsibility may well conflict with a wider national concern for translocal benefit or more general protection from harm. This question of local difference discussion not only against the background of social effects of moral relativism, but also against the background of priority - setting when two ideals are in apparent conflict.

In such discussion, particularly with members of this present international group, Professor Dunstan's concern for the middle ground (used in his context as between public and scientist autonomy on the one hand and paternalism on the other) is most relevant. Until there is national consensus on certain ethical issues, the possibility for transnational agreement is most difficult. In that context, there is need for this group to encourage further national-local consultation in the areas of research interest even as the discussions towards national-international interdependence proceed.

It seems reasonable to argue that the international public will draw from the national public even as the latter draws from the local group. The strength of international development here can come only from respect for difference at both national and local level. Stated differently: the way in which an international group shows respect for local or national autonomy, while yet seeking to advance benefits and prevent harm globally, will set the stage for local and national activity, even as it furthers the international goals desired.

In conclusion, and with reference to the questions of non-research and local-national-international research ethics, if autonomy is to be preserved, it appears that benefit may suffer and harm may increase. If benefit versus harm is the basis for ethical decision-making, then autonomy, may suffer. Ultimately, resolution regarding decisions about research to be done goes back to the public opinion, as mentioned by Professor Dunstan. Such a stance is not without difficulty, however. Is such public opinion to be left alone so that matters are settled by open debate and those responsible for individual ethics committee decisions are to be influenced locally by such debate?

Document 5

MECHANISMS OF ETHICS REVIEW
LES MECANISMES DE L'EXAMEN ETHIQUE

Raymond Hoffenberg

Discussion: Charles McCarthy
Shigeaki Hinohara
Henry Friesen

Session E / Séance E

International Summit Conference on Bioethics
Colloque international de bioéthique

Mechanisms of Ethics Review

PRESENTATION: Raymond Hoffenberg

The need to protect the subjects of research was recognised in the Declaration of Helsinki (1964) (1) and the report of the Medical Research Council in the UK (MRC) (1962-63) (2). Neither statement provided guidance about the way in which controls might be introduced or monitored. In 1967 the Royal College of Physicians of London (RCP) recommended (3) that all clinical research investigations should be subject to ethical review and proposed that committees should be formed in each district of the country specifically to carry out this function. (For administrative purposes England and Wales are divided into approximately 200 districts). This proposal has effectively been implemented.

The majority of these Ethics Committees (EC) are based within hospitals, especially teaching hospitals, in which most clinical research is conducted. Most EC's have assumed responsibility for monitoring all clinical research carried out in their districts and receive applications from general practitioners, pharmaceutical companies and others who wish to carry out research in the community, as well as from hospital-based research workers. In some instances an EC established within a single hospital will confine its interests to research carried out within that hospital. In such cases the control of research in the community may be less than adequate.

Three times in the past decade Chairmen of district EC's have met to discuss problems of common interest and ways in which their activities might be refined to ensure that proper protection is provided for the subjects of research without, at the same time, imposing such strict constraints that the advancement of medical knowledge would be impeded. At the second meeting of EC Chairmen in 1982 the RCP was asked to collate information and opinions on a range of matters concerning the constitution and mode of practice of local EC's. A set of guidelines for their practice was published by the RCP in 1984, (4) many recommendations of which form the basis of this presentation.

Membership of EC's

The RCP recommended that committees should be comprised of medical, nursing and lay members. In practice, most EC's now have roughly equal numbers of medical and non-medical members. They should be chosen not because they are experts in moral philosophy but as "people of goodwill with a high regard for the human personality, for truthfulness and for the continued advance of medical science". The quality of individuals matters, not that specific groups or organisations should be represented.

Increasingly, the importance of lay members has been recognised. Even if their understanding of detailed medical issues may be limited - as might equally apply to some of the medical members! - they provide invaluable general advice, particularly on such matters as consent and other safeguards for the subjects of research.

EC's should be of manageable size, usually less than twelve members. Alternates should be available to ensure a valid quorum; this should always include one or more of the lay members.

Matters to be considered by EC's

The RCP firmly recommends that all research projects involving human subjects should be submitted to EC's for approval, however trivial they might seem. This would include the use of fetal material or studies carried out on the recently dead.

Optional submission cannot be justified; nothing less than mandatory review of all procedures is acceptable.

EC's must satisfy themselves, inter alia, that:

(1) The objectives of the proposed research are justifiable in the interests of the community.

(2) The information cannot be obtained in other ways, e.g. through animal research.

(3) The design and method of the proposal is of scientific validity and the outcome feasible. This requires consideration of the number of participants, which should be large enough to produce a statistically acceptable answer, but not so large as to require the performance of redundant experiments.

EC's are expected to scrutinise research proposals before they are submitted to major funding bodies such as MRC, and should make their own independent assessment of their scientific validity. They should not depute this responsibility to the funding body.

Many research proposals are organised and funded locally. If members of the local (district) EC feel themselves incapable of assessing their scientific worth, they are encouraged to enlist the advice of outside experts.

(4) The subjects of research are protected from possible harm and their rights are protected. The risk of adverse effects should be minimal or limited. This is of particular importance where healthy volunteers are used (see publication by RCP on "Research on Healthy Volunteers", 1986) (5). The degree of discomfort or inconvenience likely to be caused to the participant should be considered, including such factors as time taken off work to take part in a study, the needs of mothers with young children to make other arrangements for their care, etc. EC's should take into account the degree of "interference" with the patient. Examples of "non-interfering" research would be the ascertainment of information from patient records (here, separate issues of confidentiality intrude); or tests carried out on excreta such as urine, or blood samples that have been taken for other purposes.

In assessing the acceptability of risk, EC's will consider whether the research offers possible therapeutic benefit to the participant or not. For instance, experiments involving the implantation of fetal brain tissue might be acceptable in the case of patients with Parkinsonism but not in non-Parkinsonian subjects.

(5) Participants are reasonably informed about the nature of the studies, their attendant risks and adverse effects. They should have agreed to take part without coercion or any other form of pressure and with the knowledge that they are free to withdraw from a study without fear of prejudicial consequences.

(6) All financial arrangements are satisfactory. It is accepted that payment may be made to subjects to cover their expenses and in recognition of the time they give to the project and any inconvenience or discomfort they might experience. EC's should satisfy themselves that the payments are not so large as to induce subjects to take risks primarily for reward and against their better judgement. Personal payments to investigators have ethical implications and must be reported to EC's, who should consider whether the judgement or integrity of the investigator is likely to be compromised. It is not thought appropriate for EC's to consider the

financial cost (value for money) of a research proposal. This is more properly assessed by the funding body.

I shall now try to answer some specific questions:

I. What is the force of EC decisions?

EC decisions have no legal force - they are guidelines. There is no legal obligation for the creation of EC's; nor is there a legal requirement for all research projects to be submitted to and approved by EC's. Three powerful general prohibitions exist, however, that are influenced by the deliberations of EC's: - in fact dependent on their approval.

(1) Through grant-giving bodies. The MRC and other responsible research funding organisations will not even consider the scientific value of a project until its ethics have been approved by a local EC. The MRC would not override the decision of an EC to reject a proposal on ethical grounds, but it reserves to itself the right to refuse to make an award on ethical grounds alone even if local EC approval has already been obtained.

It is recognised that prior assurance of funding or a strong recommendation on scientific grounds from a body like the MRC might unduly influence an EC to approve a project. For this reason local EC approval should always be a prerequisite for submissions to funding bodies.

(2) Through institutions in which research is carried out, e.g. universities or hospitals, which may exert their rights as employers not to allow non-approved research to be carried out on their premises.

(3) Through medical and scientific journals, which may refuse to publish research papers that do not expressly state that ethical approval has been obtained. Most reserve the right to reject a manuscript on ethical grounds alone even if EC approval has previously been obtained. The majority of journals dealing with clinical research publish a clear policy statement about the need for EC approval.

The application of these three forms of control will persuade most research-workers to seek prior and proper approval from EC's, but there are loopholes for exploitation by less rigorous or scrupulous investigators, especially those who do not work in the University or NHS systems.

Although the existence or satisfactory functioning of EC's is not legally enforcible in the UK, the Government has strongly encouraged their creation. The Department of Health and Social Services (DHSS) circulated the original RCP report widely and gave advice (in 1975) that was largely based on it.

II. Are EC's accountable?

From hearsay evidence it seems that most EC's deal responsibly and properly with applications that are submitted to them, and apply adequate controls over research done within their districts. Some, it is rumoured, take their responsibilities less seriously and "rubber-stamp" applications that reach them from their own consultant staff. Others, it is alleged, fail to meet, so that research is carried out without any ethical appraisal.

The impression is that the vast majority of EC's function well, but in the UK there is currently no mechanism for monitoring the performance of EC's or even for ensuring that they exist in all districts. It has been suggested that their establishment and the need for all human research to be submitted to them should be subject to legal enforcement. This would not be too difficult to arrange, but it would be difficult to assess the quality of the judgement made by individual EC's. Much would depend on the quality and responsibility of its members.

III. Should there be a Central (National) Ethical Committee?

So far, the idea has been rejected. It is frequently argued that local EC's reduplicate work by being required independently to assess research protocols that might already have been approved or rejected by other EC's. A central committee would be able to amass a bank of information about various types of research procedure and could make its collective judgement available to local EC's. It would also more readily have access to national or international experts who might be prepared to respond to a single central co-ordinated request for advice but not to multiple similar requests emanating from a large number of independent EC's. While this concept has merit as a source of information for those who seek it voluntarily, a national committee could not, and should not, impose its directives on local committees whose knowledge and understanding of local investigators and their circumstances might allow more judicious appraisal of their applications. It is important for the autonomy of local EC's to be respected and this should rarely, if ever, be subject to imposed control.

There are circumstances, however, in which a central or national view might be helpful. In large-scale clinical trials, for instance, - especially those involving rare diseases - it is usually necessary to recruit subjects from many different centres. The organisation of such trials might be seriously disrupted or delayed by the need to seek approval from each and every participating centre independently. In such a case, it should be possible for the trial-organisers to submit the proposals to a properly-constituted ad hoc central committee, whose views on both the ethical and scientific nature of the study might be circulated to all participating centres as a guideline - not as a directive.

No national scheme should replace the mandate of local committees to evaluate all projects to be carried out in their own institutions or districts. Too-ready acceptance of national guidelines might result in less careful assessment of local factors and eventually to downgrading of the status of local EC's.

In several countries there are national committees that consider more general questions about the social acceptability of research or other matters of ethical importance. In Sweden, for instance, a committee was established in 1985 to give a "rounded" view of questions concerning medical research and "issues of human integrity...and respect for human worth". (6) It has a wide remit and acts as "a mediating authority between science, popular opinion and those politically responsible". In France a larger permanent advisory committee has existed since 1983 "to give advice on the moral problems arising from research in biology, medicine and health, where these problems concern individuals and groups or the whole society". (7)

No such committee exists in Britain. There is, however, a consortium of Royal Medical Colleges and Faculties which meets quarterly as a "Conference". The Colleges·have a long tradition - in the case of my own Royal College of Physicians going back to 1518 - of concern for standards of medical practice and the monitoring of professional ethics. They are not medical trade-unions, nor do they act as disciplinary bodies for the profession. They have, in fact, no statutory power over doctors and rely simply on respect for the guidelines they issue from time to time. Their existence, however, provides an interface between Government and the public, which still commands the respect and confidence of the public. Government tends to use the Colleges and their Conference as a sounding-board on ethical issues and, when appropriate, asks for their advice about specific problems.

I shall give two examples:

(1) Heart transplantation

Heart transplants were first carried out in the UK in the late 1960's. In late 1972 the Chief Medical Officer (CMO) convened a group of experts drawn from Conference and communicated their recommendations in 1973 in a letter which effectively constrained the development of heart transplant programmes in the UK, on the basis that the technique was still largely experimental. In accordance with these recommendations, progress in the field was closely followed by a special Advisory Panel composed of wide medical representation. At the same time the DHSS asked Conference to consider criteria which would indicate permanent functional death of the brain and therefore allow mechanical ventilators to be switched off. In 1976 Conference issued a statement including conditions for diagnosis of brain death and tests for its confirmation.

In 1977 the Panel advised the CMO that the results of cardiac transplantation now justified its introduction into NHS practice. This plus the College's criteria for brain death led to the establishment of a few designated centres to carry out a programme. On professional advice, three centres were approved, a fourth has recently been recommended.

At various times in the past 10 years Conference has re-examined and refined its criteria for brain death and the DHSS in 1983 circulated guidelines to all hospital doctors based on Colleges' views entitled "A Code of Practice" and intended as a "set of basic guidelines which could be amplified to suit local circumstances".

Towards the end of 1986 a heart transplant operation was carried out on an infant using an organ taken from a newborn anencephalic baby. The DHSS was concerned about ethical aspects of this operation, including the application of brain death criteria in neonates in general, and the difficulty of establishing the moment of death in anencephalics, in particular. They asked the Conference of Medical Royal Colleges and their Faculties to consider these problems. A working-party of Conference met and immediately recommended a moratorium on all transplantation from and into infants up to the age of one month, while its report and recommendations to DHSS are being prepared. In his letter of 10 February 1987 to all Regional Medical Offices, the CMO accepted the wisdom of a moratorium and said "I hope it will be heeded by all transplant surgeons". It is important to note the tone of this statement, which is clearly not a directive, simply an expression of hope.

(2) In vitro fertilisation (IVF)
The first child resulting from IVF was born in July 1978. The MRC set up an advisory group in that year to review policy on research related to IVF and pre-embryo transfer in humans. Guidelines were published in 1982 (revised in 1985).

In 1982 the Government established a Committee of Inquiry into Human Fertilisation and Embryology which produced the "Warnock Report" (named after its Chairman) in 1984. One of its main recommendations was that a statutory licensing authority should be established to regulate research and certain types of infertility services. Recognising that it would probably take time for the necessary legislation to be enacted, the MRC with the Royal College of Obstetricians and Gynaecologists (RCOG) agreed to set up, as a temporary measure, a joint Voluntary Licensing Authority (VLA). This authority met for the first time in March 1985. It consists of 14 members, 7 of whom, including the Chairman, are non-medical lay members. The guidelines drawn up by the VLA are intended to set minimal acceptable standards as a basis for local EC's to agree "their own house-rules".

Again, the nature of this process should be noted. It was the profession that advised the formation of a Statutory Authority and took the initiative in establishing a joint VLA, and it is the voluntary acquiescence of EC's and their research institutions that has effectively regulated the conduct of IVF and research involving human pre-embryos. The role of Government has been to advise and facilitate, not to impose.

I hope this gives the flavour of the way ethical problems are dealt with in the UK.

The emphasis is on decisions made locally through a process that depends on integration of non-medical lay people in the process.

This and the special and privileged role of the Royal Colleges has preserved the confidence and trust of the public, without which no system of ethical review could be sustained.

(1) Declaration of Helsinki, 1964, report of World Medical Assembly.

(2) Medical Research Council. Responsibility in investigations on human subjects. Report of MRC 1962-63. (2382).

(3) Royal College of Physicians (1967). Supervision of Ethics of Clinical Investigations in Institutions.

(4) Royal College of Physicians (1984). Guidelines on the practice of Ethics Committees in Medical Research.

(5) Royal College of Physicians (1986). Report on "Research on Healthy Volunteers" in Journal of RCP 20, 3-17.

(6) Statement from Swedish Ministry of Social Affairs (Lene Jonsson, 5 March 1985).

(7) Decree signed by the President of the Republic of France in February 1983.

Document 6

ACCOUNTABILITY OF THE ETHICS REVIEW PROCESS
DE QUI RELEVE LE PROCESSUS D'EXAMEN ETHIQUE?

Vittorio Sgaramella

Discussion: Charles McCarthy
Shigeaki Hinohara
Henry Friesen

Session E / Séance E

International Summit Conference on Bioethics
Colloque international de bioéthique

Accountability of the Ethics Review Process

PRESENTATION: Vittorio Sgaramella

A discussion of the accountability of the ethics review process should clarify the interconnections between the bodies called to exert such review on one side, and on the other a variety of relevant institutions, structures, groups and individuals. These latter could be the targets for ethically ambiguous experimentation, could actually perform or allow others to perform the experiments, or finally could hold decisional powers as to their regulation and funding. The resulting interrelationships are already rather intricate. They could be further complicated because of different religious, political and cultural milieux. This is so even when the problems arise in technologically advanced Countries which by and large share similar sets of values.

Discussion of the accountability of the ethics review process must rest on the preliminary elaboration of a few points, some of which could be considered culturally invariant:

1. the definition of the subject of discussion;
2. the identification and the evaluation of the problematic areas;
3. the values which are at stake, and the standards according to which they should be measured and possibly safeguarded;
4. the levels and the modes by which the review process(es) could best be accountable, given the parties involved and their interrelationships.

The conclusions of this discussion should lead to the elaboration of specific indications as to the measures to be adopted to make accountable to society the whole ethical review process in biomedical experimentation.

As for point (1), it is clear that the term "ethics" is here strictly limited to actions performed in the field of biomedicine and biology; in other words we are dealing with "bioethics". Bioethics is a neologism introduced to describe a discipline which has grown substantially since the late sixties: its purpose is to provide answers to some novel questions raised by recent progress of biological research. It is important to emphasize that it embodies the traditional medical deontology, rooted on the Hippocratic Oath, and in more modern times formulated in statements like the Nuremberg Code and the Helsinki-Tokyo Declarations; but for the novelty of some issues, it transcends it. The scientific events which have most stimulated the elaboration of this novel discipline are twofold:

a. the ability to perform human reproduction in vitro and, to a certain extent, to manipulate it, and
b. the ability to transplant into living cells genes of various origins, including genes which are foreign to the evolutionary history of the target cells. Such exogenous genes can be incorporated in the genetic endowment, or genome, of the manipulated cells and thus be transferred to future generations.

Since the latter is usually referred to as "genetic" engineering, it could be proper for the sake of coherence and simplicity, to indicate the former as "reproductive" engineering; but we should be aware that the suspicious shadow which accompanies the latter might also mar the image of the former. These two forms of "engineering" although presently unrelated, could well be brought together, resulting in ethically complex issues.

Since the beginning of '70's, both technologies have become important additions to the armory of biomedical and biological scientists. They are now established procedures, capable of conferring on man a considerably stronger power, as compared to that of a few years ago, over reproduction, global gene pool composition and possibly evolution, both in qualitative and in quantitative terms. The use of these technologies in general does not require very complex and expensive machinery or experimental structures; therefore although at present employed only on a limited scale, they could become rapidly more widespread, and thus bring about unforeseen, initially almost unnoticeable effects and later hardly reversible consequences.

While the pressure for the development and use of both "genetic" and "reproductive" engineering becomes more and more intense in response to their attractive scientific, medical and industrial applications, the public and an increasing number of experts are expressing a disturbing feeling of uneasiness and even fear. This feeling relates to the possibility that an uncontrolled diffusion and an increasing sophistication of the two techniques could elicit harmful effects or at least undesirable social backlash, in case of real or supposed wrong-doings. To reduce their likelihood, careful reflection must clarify the ethical issues which are at stake, and in the process help to elaborate forms of guidance, which may range from guidelines to legal prescriptions. This is highly desirable if we want to maximize and to generalize the unquestionable benefits associated with them and to reduce below an acceptable threshold the risks which are as yet largely hypothetical and/or likely to affect relatively few individuals in most instances.

Pharmacological experimentation and neurobiology are also areas dense in ethically problematic issues. Among the most serious of these are: the informed and free consent to experimentation, the use of animals in research work, the attention to the needs of patients affected by rare diseases or poor in economical resources, like those from Third World Countries, the concept and use of placebos, the boundaries between somatic and emotional-intellectual spheres. These and other related topics will not be further discussed here to avoid likely duplications with other presentations.

In the preceding scheme, point (2) calls for the identification and evaluation of specific problematic areas. In reproductive engineering these area generally identified as follows:

a. the commercial donation and storage of human gametes, so far mainly of sperm but with the possibility for ova as well;
b. the separation of sperm into Y-containing (male producing) and X-containing (female producing) gametes, to be used in sex predetermination of the child-to be born.
   This technique could be desirable in the case of mothers heterozygous for a recessive X-linked genetic disease (e.g. hemophilia A and B, Duchenne muscular dystrophy): the use of X-containing sperms would allow the birth of females only, who have thus 50% chance of being free of the disease causing gene and 50% chance of carrying it, but in a heterozygous symptom-free condition. The diffusion of the relevant techniques could lead in the long range to a distortion of the sex ratio in the population;
c. the fertilization of oocytes either in vitro or in vivo, following admixture with homologous (husband) or heterologous (donor) sperm;
d. the interventions on the embryo, like transfer, splitting, microinjection, storage length and conditions: commercial uses of embryonic or fetal tissues, cloning of individuals;
e. the right of single females to generate children through artificial means, even of the "do-it-yourself" type, possibly secured under the anonymity of mail-orders;
f. the moral and legal status of the zygote, the embryo and the fetus, and thus his/her fate in the case of the multiple fertilization, presently required by or at least highly recommendable because of the otherwise low rate of success of in vitro operations and the consequent impracticability to reimplant all the produced embryos in a mother's womb;
g. the spread of "surrogate motherhood" or the development of artificial placentas;

h. the interspecific fusion of human gametes.

In genetic engineering, on the other hand, it is customary to distinguish issues specifically related to man from those potentially affecting other components of the biosphere. The former could include therapeutic as well as non-therapeutic interventions. Among the former, the issue of gene therapy is of primary importance, but at present rather theoretical. It is nevertheless useful to try to anticipate some of the problematic aspects. It should be immediately recognised that any manipulation of somatic cells, e.g. bone marrow cells, performed in order to treat genetically determined conditions (from the Lesch-Nyhan syndrome, caused by the lack of the enzyme hypoxanthine-guanine phospho-ribosyl transferase, to the SCID, or Severe Combined Immuno-Deficiency, caused by lack of the enzyme adenosine deaminase), is ethically comparable to any intervention on other somatic components like heart or kidney, etc. and thus falls under the traditional deontological obligations of the operators. At present, it is possible also to perform genetic manipulation of germinal cells. The procedure is similar to that used on somatic cells and technically it too is still rather rudimentary. The heaviest limitation again is that of "targeting" the correct gene in the exact chromosomal location of the wrong one, which optimally should be removed and replaced with single nucleotide precision. Using any of the presently available techniques (microinjection, calcium phosphate-mediated DNA uptake, retroviral vectors), the efficiency of the exact substitutive targeting is still several orders of magnitude unsatisfactory. Furthermore, gene therapy on germinal or embryo-fetal cells is clearly made less desirable and less probable by the simple fact that the product of fertilization could be aborted, or even not produced, in case appropriate diagnostic procedures, performed on parents and/or on the embryo itself, give early evidence of the presence of severe genetic defect(s).

Furthermore, gene manipulation of germinal cells suffers from a therapeutic viewpoint of the drawback of possible genetic damage imposed on the cells. Such changes, most likely detrimental, if affecting the germinal line could be transmitted to the following generations with the danger of a harm greater than the intentional cure.

Among the non-therapeutic genetic interventions which are considered ethically ambiguous, we should also remember the description of the genetic constitution, or genome, of single individuals. This can be achieved at the level of a gross genetic map, based on DNA polymorphisms of the kind provided e.g. by the restriction fragment lengths (RFLP), and could at least theoretically reach the detail of the complete sequence of the 3.0 billion base pairs constituting the haploid human genome.

The genomic map is already being used in important medical applications like the pre-natal diagnosis of pathological conditions caused by mutations in yet unidentified genes which happen to be closely linked to (and thus segregating together with) polymorphic genetic markers like RFLPs. Other interesting applications are being introduced, for example, in forensic practice. These help paternity or familial disputes and in the identification of criminals, even when only small samples of the individual's nucleated cells are available.

Whereas such applications are clearly very useful and their development and diffusion are welcome, the obligation of confidentiality in their use remains obvious, in analogy with the acquisition and storage of information on other medical conditions. This applies also to the possibility, at present at least a decade away, of obtaining the complete sequence of a human genome. Without embarking in the dispute presently raging among molecular geneticists on the appropriateness and usefulness of such a mega-project, it should be stressed that the knowledge of the total genomic sequence of an individual would in general provide information more useful for the advancement of human genetics, than for the benefit of the patients/subjects involved. It is important though to emphasize that the information stemming from appropriate RFLP analysis, or, even better, from the whole DNA sequence could also allow the prediction of diseases likely to manifest themselves only in later years of the carrier's life, well after the reproductive age, as with Huntington chorea. In this case, as in others, it is not clear whether it is ethically desirable to perform such analysis and inform the possible future patient of (a) his/her conditions; (b) the fact that their children could develop the disease in an often distant future; (c) the present lack of effective treatment. It is desirable that collection, storage and availability of such information satisfy primarily the requirements of benefit to the patient and not of his/her descendants, nor of scientific knowledge. It should indeed be borne in mind that any information which is not explicitly useful, could be detrimental: for instance an unfair use of such information by employers or insurers or others should be discouraged, but the chance for this to happen should be balanced against the foreseeable advantages, if any, to the individual.

Another aspect of genetic engineering which is also ethically ambiguous is the uncontained use of genetically manipulated organisms for agricultural, extractive, or ecological purposes.

Whereas the use of genetically manipulated microorganisms in physically contained industrial plants can be looked at satisfactorily from the bioethical viewpoint, the issue surrounding the release of genetically engineered organisms in the environment is still charged with emotions as sound preliminary information is lacking. The indisputable facts which have to be borne in mind are that a) ecological boundaries are thinner and different from national borders and that b) ecological equilibria are very fragile.

Coming to point (3) of the list given at the beginning, in the case of biomedical experimentation the values which are at stake in the bioethics review process are generally acknowledged to be the integrity, the freedom and the dignity of the life of the individual from the initial moment of life to that of death. Such a statement elicits immediately a variety of problematic issues: most prominent among them, how to define both the beginning of an individual life and its termination. The simplest approach to the definition of the beginning of human life is probably the fusion of the male and female pronuclei following the fertilization of an oocyte by a spermatozoon. But even if we accept this precise phenomenon as the most relevant for the beginning of an individual's life, we cannot ignore that a variety of problems remain to be solved: e.g. it is difficult to recognise rationally a human being in a single cell-zygote or even in a multicellular blastocyst. Early embryonic masses undergo divisions which bring about the appearance of different structures called embryoblast and trophoblast: the former produces the embryo, the latter, inter alia, the placenta. Even if we were to distinguish them before their differentiation, we would not treat them differently. Yet, after differentiation, and specifically at birth, obstetricians discard placenta and umbilical cord, unquestionably endowed of "life", but obviously save the new-born. Also, from the occasional splitting even of a 14-day embryo twins could be formed. This raises the issue of when the resulting individuals do actually appear. Furthermore, during the time of fertilization, degenerative processes can occur at the chromosomal level of the embryo, and give rise, for example, to a very dangerous tumor, the chorio epithelioma. In this case fertilization generates, or rather, degenerates into, something antithetic to life to the point of representing a fatal risk to the mother. Of similar relevance is the problem of death. The importance of its definition affects not only the existence of the person involved, but also, in the case of removal of organs for transplantation, the survival or at least a better life for other human beings. The reliance on all means to prolong life is a fundamental right of every human being; and so is the possibility of facing death in a dignified way.

The problem of organ transplantation should be considered as a contingent one. It is ethically at least ambiguous to plan the cure of a patient on the premature death of another human being, whose body, as soon as an "official" death (to be based on brain? or on heart?) can be declared, is dissected for the recovery of organs, sometimes even in spite of the donor's explicit refusal to donate. Greater support should be given to the development of artificial organs, the only humane answer to the necessity of organ replacements.

A value of importance secondary only to those of the respect of the human person should be the integrity and evolution of the global gene pool. Attempts to alter it in uncontrolled ways should be minimized, keeping clearly in mind, though, that nature on its own is continuing to perform its experiments, which can lead also to results harmful to mankind. An example of this is the appearance of the HIV viruses responsible for AIDS: to cope with such unforeseeable events is only possible through farsighted generous support of basic biomedical research.

Protection of the global gene pool raises also the issue of protection of the natural environment. The latter is critical for many reasons, among which are the concepts of preventive medicine against physical, physiological and genotoxic damages.

The issue of basic biomedical research raises another point in the ethics review process: fraud in scientific research. The examples of faked data are becoming more and more numerous in biomedical research, probably more than in other scientific disciplines. This could be due to an intrinsic variability of the biomedical experimental systems, less amenable to rigorous controls than in other areas, but mostly I believe to the greater pressure to publish as much as possible, typical of this field where it is an important prerequisite to career advancement and/or to professional promotion. The ethical problem of scientific honesty in biomedical research deserves great attention, because of its objective damage to the progress of a given sector of investigation as well as for the tarring to both the images of the specific institution involved and the scientific research process in general. Suggestions could be made as to how to render institutions somehow co-responsible for the scientific frauds involving their members or associates.

We come finally to the last of the points initially mentioned: the levels and the modes at which the review process could best be accountable.

In view of the magnitude, the diversity and the novelty of the issues involved, it seems highly desirable that each country sets up some form of national bioethics committees, where all the various expertises, potentially involved, are represented. Side by side with medical doctors, there should be pharmacologists, biologists, geneticists, ecologists, theologians, psychologists, lawyers. Lay people should also have a fair representation because of their lack of vested interests in the discussion matter and of their unorthodox perception of the problems under scrutiny, and especially of the unexpected ones.

In close connection with the national bioethics committees, at least the major universities and medical centres should set up institutional bioethics review committees: their specific tasks should be the discussion of specific and local bioethical issues faced in the normal activity of the institution and an attentive and sensitive response to the issues surfacing from their day-to-day work. It is of paramount importance that hypersensitivity and sensationalism are avoided, but not at the price of openness and thoroughness: mass-media involvement should be solicited since it could be extremely useful if carefully monitored by conscientious and reliable professional expertise, which is too often pitifully offended. Wide public participation is essential at this stage: scientific truths are not reached by majority votes but scientific policies might be, especially when social and ethical issues are involved. Experimentation on human subjects/patients, at least for the time being and possibly for some time to come, is presenting issues characterized more by ethically relevant than by scientifically defined problems.

In the present phase, it is likely that accountability can be best obtained through a wide spectrum of measures. Among them:

1. Activation of Institutional Bioethics Review Committees (I.B.R.C.) in all major Hospitals and Research/Care Institutions. In Italy they are just a precious few and more are badly needed.

2. Registration of all Institutions interested and capable of performing ethically ambiguous biomedical experimentation, by a central authority like the National Health Institutes;

3. Creation of a National Bioethics Committee, possibly including also the Chairpersons of the I.B.R.C.

4. Organization of international authoritative forum like this one.

5. Public and frequent discussions and analysis of the relevant problems at local levels.

6. Greater emphasis on bioethics in the curricula of biomedical students.

In conclusion, it seems apparent that the new biology emerging in the last quarter of this century is shaping and presenting a new concept of man, as well as a new concept of nature. Bioethics should take into proper account their commonalities and peculiarities, and strive to secure the fullest possible satisfaction of human needs and rights in harmony with nature and culture, both in continuing and often conflicting evolution.

But we must keep clearly in mind that if it is true that culture is changing and clearly it does so with an accelerated pace, especially if compared to nature, and so does morality. But this does not mean that ethics must also be similarly changing. The basic principles of a bioethical code are not changing, or at least should not be changing much faster than, say, the rate of change of the human genetic code. Otherwise what we achieve here by the end of the week will not be valid at our next meeting in 1988.

We must strive to reach a consensus on the definition of a set of basic principles which can give strength and credibility to our recommendations and standards.

These principles should give full protection to the human being, not necessarily only on a personalistic basis, but also in view of the protection of the entire human species inclusive of the unborn, which is entitled to a healthy genetic constitution if informative diagnostic and therapeutic procedures are available, or can be made so.

Documents 5 and 6

PROCEDURES IN IMPLEMENTING NATIONAL STANDARDS FOR RESEARCH WITH HUMAN SUBJECTS
APPLICATION DES NORMES D'ETHIQUE EN RECHERCHE SUR DES HUMAINS

Discussion: Charles McCarthy
Shigeaki Hinohara
Henry Friesen

Session E / Séance E

International Summit Conference on Bioethics
Colloque international de bioéthique

Procedures in Implementing National Standards for Research with Human Subjects

DISCUSSION: Charles R. McCarthy

Mr. Chairman and distinguished colleagues, Sir Raymond Hoffenberg of the UK has presented a clear and comprehensive description of the current methods employed in his country to protect the rights and the well-being of human research subjects in the United Kingdom. I note many similarities as well as marked differences between the British system and that employed for similar purposes in the United States of America.

Professor Vittorio Sgaramella of the Italian delegation provided an eloquent appeal for increased accountability in the conduct of research involving human subjects. He has directed particular emphasis to reproductive technologies and potential research involving genetic interventions while focusing attention on a number of general principles common to all research involving human beings. Prof. Sgaramella has recommended national bioethics committees to deal with transcendant policies as well as local committees created to address more circumscribed problems at major universities and medical centres.

Rather than comment in detail upon these excellent papers which speak for themselves, I should like to describe the system which has evolved within the USA. This system, now entering the third decade of its existence is one which I know first hand, and one which is similar in some ways to those described in the two papers, but also one which manifests its own national characteristics as well.

The fact is that the U.S.A. employs not one, but two parallel and closely coordinated systems for the protection of human subjects of biomedical and behavioural research.

The first system, set forth in a statute couched in general language, is implemented by flexible regulations which enjoy the force of law but which can be updated as needed. The regulations provide the flexibility which is necessary for a system which must adapt to ever-increasing complexity in research funded by the US government. This system pertains to research projects involving more than $6 billion in Federal support each year. The statutory authority set forth in Section 495 of the Public Health Service Act and implemented by regulations (45 CFR 46) requires each institution engaged in research supported in whole or in part by Federal agencies to provide written assurances to the funding agency that:

1) It has adopted a statement of principles governing all agents of the institution in the conduct of research involving human subjects.The cited principles may be set forth in the Helsinki Declaration or other internationally recognized Coses, but in nearly every case US institutions subscribe to the Belmont Report which explicitates three ethical principles set forth by the National Commission for the Protection of Human Subjects. These principles are: (a) respect for persons; (b) beneficence; and (c) justice. They are reflected in the regulations by: 1) requirements for obtaining and documentation of informed consent; 2) the requirement that risks be reasonable in the light of expected benefits of research and the knowledge to be gained; and 3) equitable distribution of both the risks of research and its benefits throughout society.

2) Establishment of a local ethical committee which is called an institutional review board (IRB) which serves as an agent of the institution in prospectively reviewing and approving each research project and in conducting continuing review of those projects already approved. Approval by the IRB does not commit the institution to conducting proposed research, but disapproval serves as a veto which may not be overridden by any official or group of officials in the institution.

3) A list of members and their qualifications to serve on the IRB. The list must include: at least five members including at least one woman; one or more scientists; at least one non-scientist; and at least one member not affiliated with the institution in any other way other than through service on the IRB.

4) Written procedures -- shared with all persons in the institution involved in research -- that the IRB will follow.

This assurance document commits the institution to a responsible course of action approved by the Office for Protection from Research Risks within the Department of Health and Human Services, and requires the institution to make sure that its agents function appropriately in conducting research with human subjects.

The regulations require institutions to provide additional assurance of protections for vulnerable populations including pregnant women, human fetuses, prisoners and children.

The institution's Human Subjects Assurance document must be approved by the US Department of Health and Human Services before any research involving human subjects can be funded by Federal agencies.

This first system governs institutions, IRBs, research investigators, administrators and members of health research teams that receive federal support for research involving human subjects.

The second system is similar to the first. However, instead of applying to institutions that receive Federal funding for research, it applies to investigational drugs, devices, biologics, food additives, diagnostic devices and other articles whose safety and effectiveness must be demonstrated in research or testing with human subjects. Before any of these articles can be marketed in the USA they must be tested in research involving humans. That research must be reviewed and approved by an IRB prior to testing in humans. As in the system described above, informed consent, risk/benefit analysis and continuing review are required by regulations which implement the Food, Drug and Cosmetic Act.

Both systems require an elaborate process for obtaining informed consent process, recording of IRB minutes subject to Federal inspection, documentation of adverse effects and report of injuries. Both sets of regulations require institutions, sponsors of drugs and devices, and research investigators to share responsibility for protecting the rights and welfare of research subjects. In each system, shared responsibility is stressed but final responsibility remains with the research investigator who interacts directly with research subjects.

Both systems allow for appeal to a second IRB in those rare cases where decisions of IRBs are challenged. (Less than 1% of protocols are disapproved, but approximately 44% of submitted protocols are modified by IRBs.)

These systems include about 3,000 IRBs which oversee research in our large country which supports research involving several thousands of institutions and more than 15,000 research projects involving human subjects at any given time.

The second system allows acceptance within the USA of articles such as drugs and devices tested in countries outside the US providing that the Helsinki Declaration is honoured in that country where the test occurs and providing that adequate data supporting safety and efficacy of the test article is submitted to the US Food and Drug Administration.

The dual system is guided by broad policies developed by Commissions that have functioned at the national level. These include: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, The President's Commission for the Study of Ethical Problems in Medicine in Biomedical and Behavioural Research; Ethics Advisory Boards (standing and ad hoc); the Office of Technology Assessment (U.S. Congress); The Federal Coordinating Council for Science, Engineering and Technology and the proposed new Congressional Ethics Committee.

Mr. Chairman, these remarks provide only a brief summary of the methods employed by the USA to protect human subjects. As you can see they are characterized by accountability, responsibility, universality, and partnership between the Federal and the private sector. I will be pleased to answer questions about this system as the discussion continues.

DISCUSSION: Shigeaki Hinohara

Remarks on the paper "Mechanisms of Ethics Review"

I understand, in 1967 the Royal College of Physicians (RCP) published a recommendation that all biomedical research involving human subjects should be reviewed from an ethical point of view. It is generally understood that this lead to the establishment of local Ethics Committees, mostly based at teaching hospitals, in a number of administrative districts in Britain.

From his own experience of running the E.C.'s, Dr. Hoffenburg has indicated various points which ethic committees may face in order to function properly, and has made a number of suggestions as well as solutions. These are all very valuable information and we are truly grateful.

I would now like to discuss to what extent can these suggestions be adapted in Japan and what difficulty do we foresee in terms of our cultural and social background.

Organization of Ethics Committees

I think it is beneficial that ethics committees are based at medical schools or medical research institutes and teaching hospitals as most of the research is conducted within their premises. This is exactly the way Ethics Committees or Institutional Review Boards are established in Japan at the moment. The report said that E.C.'s in Britain have twelve members in average, but the Japanese counterparts have a varied number, ranging from five to twelve; the average being eight. Contrary to the E.C.'s in Britain, the majority of the members are faculty members of the medical schools or medical research institutes where the committee is based. Outside members are very limited: mostly only one or two if any. The largest number of outside members in a committee being four out of ten, and this is an exceptional case. In Britain it is obligatory to have nurses as members, but in Japan there is practically no committees with nurses' participation: the only exception being a teaching hospital where I belong.

Dr. Hoffenburg suggests that medical and non-medical members should have an equal representation in a committee and says that the E.C. members should be selected "not because they are experts in moral philosophy but as 'people of goodwill with a high regard for the human personality, for truthfulness and for the continued advance of medical science'. The quality of individuals matters, not that specific groups or organizations should be represented." I fully agree with him, but whether this equal representation is appropriate or not, in the light of reducing the risk of the subjects and enhancing the biomedical sciences as outlined by the Declaration of Helsinki, depends on the cultural and social awareness of the adopting nations. The composition of the committee will have a significant meaning for the future role of E.C.'s.

I support the idea of having nurses as well as goodwilled lay persons as committee members. Nurses' participation should be recommended because they know the sentiment, feelings and the way of life of patients and families better than doctors. It may be necessary to make it a prerequisite to have nurses' and lay persons' participation in any E.C.'s.

Matters to be reviewed by E.C.'s

For any biomedical research involving human subjects to be approved by E.C.'s, it is absolutely imperative that the research plans and methods are scientifically valid and that the technical standard assures safety of the subjects. It is also highly desirable to achieve the goal with a minimum number of experiments. Proper supervision must be given not to allow redundant experiments.

It is often difficult to determine how honest we should be when we inform the patients and their families about the research when we try to obtain their consent. This largely depends on the patient-doctor relationships. When relationships are "vertical", it tends to be more difficult. In societies where these "vertical" relationships are more prominent, it may be advisable to have a kind of mechanism where nurses are involved as mediators. She should be able to explain to the patients in plain words and be more approachable by the patients for any questions they may have. She will be a valuable help to obtain truly informed consent by the subjects. When research is undertaken on behalf of some external organizations, expecially pharmaceutical companies, it is likely to involve the question of payments to investigators. As an unreasonable amount of payment should have some ethical implications, this is one item which must be discussed at E.C.'s.

Ethics Committees outside the medical schools

In addition to the ethics committees based at medical schools, associate teaching hospitals should also have E.C.'s. Recommendations by such organizations as the Hospital Association will help to initiate their establishment.

E.C. and National Central Organizations

To establish a supervisory mechanism by the third party to check the operation of E.C.'s is not a simple matter. The involvement of the national government in this matter presents problems.

However, it would be desirable if the national conference of E.C. chairmen is organized, which will enable the government to obtain a general picture of the bio-ethical review in the country. I am against the idea of direct government involvement in organization of E.C.'s. However, I think it is desirable if the research institutes and hospitals that have E.C.'s would register at a certain central academic organization, (in the case of Japan it would be the Science Council of Japan). Thus each E.C. is expected to review whether its protocol satisfies the academic and ethical standards of the particular central body to which it is registered. In the case of granting government research funds, those registered research institutes should be given priority. In any case independency must be respected by all means.

It will have a significant effect on the development of ethics committees if experienced international experts meet and study its management, composition and, above all, the spheres of problems which E.C.'s should handle. It would also be beneficial if the symposia on this issue are held repeatedly throughout the world with participation by both professionals and lay people.

Membership and Composition of Institutional Review Boards or Ethics Committees

In Britain the membership averages 12 whereas it is usually more in the United States if I understand correctly. In the case of Duke University, the Board comprises altogether 33 members and 2 consultants; the former includes representatives of every major specialty of medical sciences as well as other disciplines such as nursing, psychology, law, sociology and theology. Representatives of community interests and medical students are also included. Two consultants are recruited from pharmacology and statistics.

In Japan the membership ranges between 5 and 10, the average being 8. In some cases however, Kyoto University for example, in addition to the central committee of 10 members, there are 6 sub-committees each with 6 members, in total 36 sub-committee members.

As the research involving human subjects deals with a wide range of subject matters, it is desirable that Institutional Review Board members take turns, changing the membership every two to three years, thus enabling many people to be involved in ethics review.

It is advisable that research protocols receive preliminary review by the relevant specialists to clarify any problems and make alterations or revisions they may require before they are presented to the Review Board. No protocol should be submitted for grant application unless it is approved by the Review Board.

A number of professional journals already request the ethics board approval to be mentioned in the papers in order for them to be acceptable for publication. This practice should be widely observed by every medical and scientific journal.

Remarks on the paper "Accountability of the Ethic Review Process"

In his report on accountability of the ethics review process, Dr. Sgaramella has systematically analyzed the problems pertinent to this subject and presented abundant material for us to consider. We are grateful for his valuable contribution.

Biology and biomedical sciences has made such notable advances in the recent years that within a decade, before we enter the 21st century, we will no doubt be confronted with entirely new bioethical topics which we had never even imagined until only 30 years ago. It is as if until 30 years ago no one in the world had imagined that man would travel to the moon as the space ship Apollo did.

As the result of rapid advances in medical sciences, it has now become possible to generate a human life in vitro, rather than in the female body and to predetermine the sex of a child-to-be born without expensive machinery or elaborate experimental set-ups. Even some individual obstetricians can perform these techniques if they possess some extra enthusiasm. These could be blessings to some people: the former is definitely so to a couple with sterility problem. However, to generate a human life in a laboratory is to isolate an unseparable part of the private life of a married couple which hitherto was accepted as a natural and integral unit of society. This will introduce an entirely new dimension, a variable, to the practice upon which our views of life and ethics have always depended, and will give an impression as if the traditional value on marriage, or ethics of a married couple is threatened. This is no longer a problem limited to medical researchers and physicians or couples with sterility problem or single females wanting children through artificial means. But it is a problem with grave significance presented before humanity that we are in an age when fundamental research into the solemn fact of creation of human life is an urgent requirement.

What we are now confronted with is something that the world could never foresee, perhaps only comparable to introduction of 'fire' by Prometheus to the primitive life. Therefore to cope with this new dimension in science, i.e. generation of life and its process of development, we will require a new interpretation of life based on a new philosophical as well as theological view-point. At the same time we must give serious considerations from the bioethical point of view that these techniques to manipulate human life shall not be utilized merely to satisfy scientific interests.

Today, money seems to satisfy practically every human need. But it must be questioned whether it is right that one can obtain in exchange for money, among other things, an advancement in nuclear physics which produced atomic bombs.

We should also consider the benefit of an effective information network through which ideas of various country representatives reflecting different racial, religious or cultural background are promptly communicated to each ethics committee or institutional review board. This is a matter of urgent importance and for this reason I think this conference is very timely and valuable.

The storage of human gametes, at present mainly spermatozoa, and their provision to people who desire them, is like trading the birth of a human life, and in this sense, it may have graver ethical implications that sex-predetermination. How would the conscientious public feel about this kind of experiment? Institutional Review Board's should fully reflect public sentiment in its discussion.

If we want to increase accountability of the ethics review process, it is important that crude and unprocessed research data and information are presented to the review board.

In Japan new techniques such as artificial insemination and sex-predetermination are not covered by the current Medical Practice Law, hence it will be desirable to discuss these issues at the more central level that individual Institutional Review Board's, such as the joint meeting of Institutional Review Board leaders or chairmen. Immediate government intervention will not be appropriate. The government should rather encourage the private sector to deepen discussion and build up a national consensus.

We have always understood that having a child is an evidence that both husband and a wife are given a unique ability to maintain each other lives happily in harmony. If so, advancement in medical sciences should also be properly adjusted and meet the evolving philosophy and value system of human beings. This is one of the most fundamental themes, over and beyond the discussion at a single institutional ethics committee and requires awareness of everyone of us, whether lay or professional. The general public must be fully enlightened on the issue, and such awareness should take place along with the progress of research. The public should be given full access to research information. One of the vital roles of institutional review boards is to assure this accessibility. It is therefore necessary to have as many non-medical members on Institutional Review Boards as possible, as special members, who will be able to represent humanities' viewpoint in the discussion.

Researchers are no different from ordinary citizens living in a society with their individual cultural background and may have their own religions. But once they start their research using human subjects, they see their world, the world of life sciences, through a narrow key hole, and feel an irresistible temptation to jump into that world through this narrow hole. But they must always be aware that the search into the mechanism of life is always next to danger if they neglect to recognize the value of life. It may invite similar danger as in the case of the introduction of fire to primitive life.

There is an irretrievable danger if the progress in genetic and reproductive engineering head toward production of a new human species. The human species has a history of natural evolution over the past hundreds of millions of years. Any scientist involved in life science should humbly recognize this fact and respect the great force of nature that underlies human evolution. It is a serious theme for any scientist to be humble and respect the dignity of life on one hand and pursue his scientific achievement on the other. Therefore, in addition to reviewing individual research protocols, Institutional Review Boards are encouraged to educate researchers for this purpose. It is also desirable that medical education curricula are so designed as to give sufficient exposure on this issue to medical students.

Dr. Sgaramella says in his report that 'targetting' the gene in genetic manipulation technique is still at a very unsatisfactory stage. But there must be some sort of restraint on the experiment of this technique on human subjects.

Institutional Review Boards are expected to investigate the scientific and ethical validity of research protocols. But unless they are also able to check whether the experiments have been conscientiously carried out in accordance with the approved protocols, their true value will be somewhat lost and their existence will be nominal.

Among the issues related to organ transplants, kidney transplants present little problem in Japan but heart transplants are currently in wide dispute over the interpretation of human death. It is not appropriate to discuss the issue of organ transplants without due consideration over the public sentiment toward the deceased person.

In the case of Japan, it is only in 1987, that the Japan Medical Association issued a recommendation to accept brain death as the final death of an individual. The Ministry of Health and Welfare is now carefully observing whether public consensus will be formed on this issue.

Advancement of human genetics now enables us to predict some diseases which may manifest in the latter years of the carriers' life. We must pay utmost caution as to whether and when we should or should not inform this fact to future patients. Whether anyone is entitled to predict the fate of an individual and his/her quality of life is questionable, unless there is a certain degree of guarantee that there is effective treatment and possible care for the case. Indiscriminate release of such information should be avoided, just as in the case of cancer treatment 50 years ago when there was no effective cure.

Closing remarks

I am very grateful to have had an opportunity to discuss some essential issues on Institutional Review Boards. Any medical researchers or clinicians who endeavor to contribute towards advancement of medical sciences, at the same time paying utmost respect to human rights and human lives, should discipline themselves to act righteously as professionals. A checking function such as an Institutional Review Board which will provide proper supervision is also necessary.

Medical sciences are based upon profound respect for human life and dignity. Its mission is to benefit human society. Therefore I would like to stress that anyone wishing to be a physician or medical researcher should continue to study humanities along with medical sciences. All medical schools should be encouraged to offer in their curricula sufficient opportunity to study 'medicine and humanity', where prospective researchers can learn Martin Buber's philosophy and Albert

Schweitzer's life ethics toward living creatures. The following passages illustrate how Schweitzer respected not only the lives of human beings but of animals as well. This corresponds to the spirit of Buddha in Oriental philosophy.

"Devoted as I was from boyhood to the cause of the protection of animal life, it is a special joy to me that the universal ethic of Reverence for Life shows the sympathy with animals which is so often represented as sentimentality, to be a duty which no thinking man can escape. Hitherto ethics have faced the problem of man and beast either uncomprehending or helpless. Even when sympathy with the animal creation was felt to be right, it could not be brought within the scope of ethics, because ethics were really focused only on the behavior of man to man.

When will the time come when public opinion will tolerate no longer any popular amusements which depend on the ill treatment of animals!" ('Out of my life and thought', Albert Schweitzer)

Procedures in Implementing National Standards for Research with Human Subjects

DISCUSSION: Henry Friesen

The Canadian experience in ethics review procedures, in many ways, parallels the outline that we heard this morning from Sir Raymond. There is one important exception. It is quite clear that in the United Kingdom the initiative for championing and encouraging appropriate ethics review boards has taken its origin from the professional bodies (from the Royal Colleges), whereas, in Canada, the initiative has come primarily from the Medical Research Council. Why that difference has occured in the two countries is not altogether clear. I think one reason has been that in Canada the Royal College has had less interest in research and more interest in standards and education in clinical practice.

In Canada the MRC then has taken the initiative. It initially introduced a set of Guidelines in 1978. As we heard from Justice Marshall, these Guidelines are now in the final stages of revision, enunciating a set of principles and practices that should apply henceforth if approved by the Medical Research Council.(*) As a result of these Guidelines, ethics review boards are the functional arm that has been charged with maintaining and reviewing research protocols that emanate from institutions and from investigators in individual cities and regions.

The composition of these committees is not quite as clearly specified as it is in the United Kingdom, but the general nature of the individual groups that should be part of these committees is very similar, in that the Guidelines specify that the public at large should be represented, that women should be participants, that members of the legal profession might play a useful role and so on.

The process for review at the local board is very similar again. I will not dwell on that except to emphasize that informed consent is an important element and increasing attention has been given to that area. I believe it might be helpful to focus on specific issues that are matters of concern from my perspective. These include the following:

(1) We say very frequently and readily that ethics review boards should be charged with reviewing the science: Bad science is bad ethics, as though the protocols arrive labelled bad science. Clearly they do not. Most investigators believe their protocols intend to investigate worthy matters of great

importance and indeed, if anyone has any experience with review of scientific protocols, one will recognize the great difference in opinion at times about the merits of any given proposal.

It is quite clear that by and large ethics review boards sanction and approve bad science as a matter of routine. For example, only fifteen to twenty percent of scientific protocols submitted are funded; they represent the best science. Quite clearly, not all of the proposals that are not funded are bad science. Presumably, there are proposals which are less worthy and less meritorious ranging all the way to clearly unacceptable bad science. I think the record would show that after review by peer review committees there are a number of proposals that have been approved by local ethics review boards that are in the rejected category. They are really very bad science in the opinion of the peer review committee, yet have received approval at the local ethics review board.

I am not so confident that local ethics review boards are really in a position to make a sound and favourable judgment on the value and merits of the science of a proposal. We may do ourselves and the integrity of the system some harm by saying blandly and repeatedly that ethics review boards should judge the science of a proposal and are in a position to do so given the nature of the composition of the committees particularly.

(2) Another point for discussion is should all research proposals receive approval before submission to the national funding agencies. Is this a very cost effective approach when the reality again demonstrates that only twenty to thirty percent of proposals are funded in many jurisdictions? Why should we impose this onerous task on the ethics review boards when in fact eighty percent of their effort leads nowhere?

(3) Another point I would like to make is that MRC Guidelines currently are just that. They have no force of law. They have great moral authority and happily have become widely recognized as a standard and a process in Canada by which research ethics should be judged and research proposals evaluated.

I believe that it would be very helpful in the Canadian context to have a more vigourous input from the professional bodies that have a great deal at stake in this arena, for example, the Royal College, the Canadian Medical Association and so on. I believe their enthusiastic support for and participation in the development and drafting of these proposals would broaden the base of support for these Guidelines in this country.

(4) The fourth issue to which I would like to draw attention is accountability in the Canadian context. It seems very curious that the body that is charged with reviewing the ethics of research is surprisingly not accountable to anyone. It is a board that is struck under the aegis of a dean's office. As far as I know, the local ethics review boards never issue reports; certainly if these reports do exist, they have never been collated nationally. I am quite certain that, in many areas, there are no annual reports issued. I think that this is an oversight that needs attention and remedy.

To whom then are the local ethics review boards accountable except in general to the local society and the local milieu? I believe there ought to be a more formal mechanism. It is also curious that in the Canadian context there are no formal appeal mechanisms that allow the investigator to appeal a negative decision by the local ethics review board except back to the same board that rendered a negative opinion in the first place. Elementary analysis tells me that this is an inappropriate appeal mechanism.

In the same area of accountability, the question might be asked do the ethics review boards have or should they have some legal accountability? Clearly they are very powerful bodies. A failure by the local ethics review board to sanction and approve a protocol prevents the funding of that protocol. In the final analysis they have the say about which research will or will not be done.

One area of considerable concern that we confronted with some regularity in our hearings across the country was that the monitoring of the conduct of research by investigators once approval by the ethics review board has taken place is perhaps not as complete and as thorough and as careful as it might be, especially in those cases where approval is given to long term funding of a proposal. Quite clearly, we know that the precise nature of the research that is to be carried out will vary as new discoveries are made so that a single approval by the ethics review board in year one may have no relevance to the individual research proposal that is conducted in year three, four and five. What mechanisms are in place to ensure ongoing review of new and revised protocols that are introduced during the conduct of research? I think these are areas that require attention and should be addressed more completely and discussed more extensively in the days ahead.

Document 7

RESEARCH WITH THOSE WITH RESTRICTED ABILITY TO GIVE CONSENT
RECHERCHE SUR LES PERSONNES DONT LA COMPETENCE A DONNER LEUR CONSENTEMENT EST RESTREINTE

Russel H. Patterson, Jr.

Discussion: André Boué

Session F / Séance F

International Summit Conference on Bioethics
Colloque international de bioéthique

Research with Those with Restricted Ability to Give Consent

PRESENTATION: Russel H. Patterson, Jr.

A great deal has been written about research on human subjects who have restricted ability to give consent. I would like to examine various aspects of this matter, touching briefly on children and prisoners and more extensively on the question of proxy consent in the care of the mentally incompetent. Enclosed as an Appendix are some relevant guidelines developed for physicians in the United States by the American Medical Association's Council on Ethical and Judicial Affairs, upon which I serve. Some of you may find them of interest.

In the case of children and the mentally incompetent, a consensus has been reached in much of the Western world that research should be restricted to disorders that affect these groups, such as childhood diseases in children and dementia in the elderly. If research can be carried out equally well in competent adults, it is now axiomatic that the research should never be carried out on individuals of restricted competence.

In the United States, it is a matter of law that therapeutic procedures may be peformed on children with the consent of the parents. There is no legal requirement to solicit the child's assent, and the parents may override the child's dissent. However, institutional review boards may and do require the assent of children of a certain age to participate in research projects. The question of the age at which the assent of a minor becomes important has been widely discussed. Some have concluded that minors fifteen years or older can understand as much about research as adults, and others would take age seven as a more appropriate dividing line. Since children, particularly those less than fifteen years of age, are unlikely to assert themselves against authority figures such as their parents and researchers, a minor who does decline to participate in a research project must be assumed to care deeply about the matter. We should, therefore, take a child's dissent seriously (1).

Many people have expressed concern about the idea of research on children that is not therapeutic and does not directly benefit the child that is the subject of the research. They believe that all research on children carries some potential for injury, either physical or psychological, and therefore is not appropriate unless the research subject stands to gain personally in some way. On the other hand, research on normal children is likely to benefit children as a whole, and banning all research on normal children may in the long run harm some children who otherwise might have been helped if the research had been permitted.

A middle ground is to permit research on normal children if the research would not subject the child to a risk greater than accompanies ordinary daily activity. Examples might include measuring parameters like length, weight, collecting samples of urine, hair and nail clippings, and psychological testing. Tests of a more invasive nature, such as the taking of blood samples, would be left to the discretion of the Institutional Research Review Board, who would take into account the risk, discomfort, and psychological effect on the child as well as the potential benefit to children as a group. Parental informed consent and the child's assent, when possible, must be required.

What about research on prisoners? In the past, research on prison populations in the United States reached alarming proportions. The trend at present is to stop all research on prisoners except for that concerning conditions brought about by the prison environment.

Is it conceivable that prisoners might somehow be used in research without violating ethical standards? The argument against it is that the circumstances of prison life coerce the prisoner into participation. However, it could be argued that a prisoner can give informed consent to participation in a medical experiment with freedom equal to that of a subject outside of prison. For example, it is stated that boredom in prison exerts an undue pressure on the prisoner to participate. However, pressure also affects people outside of prison. Is boredom any more of a coercion to a prisoner than, say, the threat of dying of cancer is to a patient who is thereby persuaded to participate in an experimental trial of a new chemotherapeutic agent?

The payment of money to a prisoner is an important stimulus to participate in experiments, and it has been argued that the promise of money may manipulate the prisoner and coerce him. This argument strikes against payment to experimental subjects in any context. Large sums should not be used to tempt prisoners any more than to tempt anyone else (2).

If the researcher employing prisoners as subjects accurately portrays the nature of the trial and the various risks and alternatives, then is the question of coercion sufficiently blunted? Is it possible that with adequate safeguards, a clinical experiment meeting ethical criteria for a patient population outside of a prison might also be ethical with prisoners? In fact, is preventing a prisoner from participating in experiments stripping him of whatever small amount of autonomy he still guards and may in fact cherish (3)?

Prisoners generally state that their consent to participate in a research project is not obtained under coercion or undue influence. Some even argue that participation in research gives them security from some of the violence found in prisons. In essence, in denying them the right to participate in research, we are behaving in paternalistic fashion, which is against the major trend in western philosophy. And yet the prisoners are not autonomous, and they are vulnerable to exploitation. Is this lack of autonomy sufficient to justify the degree of paternalism involved in denying prisoners the right to participate in research projects? I feel that this question deserves further exploration (4).

Every person of adult years and sound mind has a right to determine what shall be done with his own body. The modern concept of informed consent is based on this precept. However, not all adults are of sound mind. Senility, coma, depression, mental retardation, stroke, and many other disorders may rob a patient of full autonomy and prevent him or her from making rational decisions. In this case, a proxy decision-maker must consent on behalf of the incapacitated patient either to treatment or to the patient's entering an experimental protocol. The major questions are: what is incompetence for medical decision-making, who determines it, who shall serve as the proxy decision-maker, and how does the proxy reach a decision (5)?

The first question is: by what standard is competence measured? The labeling of a patient as incompetent has serious consequences since it removes health care decision-making from the patient and negates the values of autonomy and self-determination. All but emergency medical treatment then is withheld until a substitute decision-maker is found.

The suspicion of incompetence usually is raised by the health care provider or by the family. Sometimes the advanced age of the patient triggers the question. However, we probably all can agree that age alone is not the determinant of competence. Another circumstance that engenders a suspicion of incompetence is a patient's refusal to undergo a treatment or to enter a trial that the physician has recommended. Perhaps the patient chooses to go without treatment, or elects a treatment that seems inappropriate. The physician suspects incompetence. The fact is that uncooperative patients are more likely to be judged incompetent than those who are agreeable and cooperative.

Competence is not an all or none phenomenon. An individual may be incompetent to drive a car but competent to make a medical decision. With respect to medical treatment, a patient may be competent to make a decision about taking aspirin for a headache and yet incompetent to make a decision about the implantation of an artificial heart. The mental capacity to consent to medical treatment or a clinical trial is the same as that required to enter a contract. A matter to be determined is whether or not the patient has sufficient intellectual function to understand the condition and the nature of the treatment with its attendant risks. Can the patient understand the available options and the merits and the disadvantages to each?

Competence has various thresholds. If the patient can show the slightest evidence of making a choice, then he or she possesses a small degree of competence. Higher standards of competence would be the reasonableness of the choice, the capability of understanding the question at hand, and the willingness to go through the reasoning process required to reach a decision.

Since the determination of incompetence triggers substitute decision-making and decreases individualism and autonomy, it is important that the physician-scientist understand various tests of competency and the pitfalls of each. It is also important that the determination of competence be subject to some kind of control, particularly in situations where the patient is declared to be incompetent because he opposes the recommendations of the physician.

Once a substitute decision-maker is empowered to act on behalf of an incompetent, the question becomes: how will the decision-maker reach a decision? The commonly used standards are those of "substituted judgement" and "best interest".

The "best interest" standard requires the decision-maker to make only those choices that would benefit the incompetent individual. This has its shortcomings, since it may be difficult to determine the best interests of an incompetent patient in a given situation. It also affronts autonomy in that a competent individual has the right to make health care decisions that may or may not be in his or her own interest. If a substitute decision-maker applies a "best interest" standard, he automatically denies the patient his right to choose a plan that might not be in his best interest by conventional standards. It might deny the subject the opportunity to participate in a research project.

On the other hand, a "substituted judgement" standard, which allows the proxy decision-maker to make a decision approximating that which the incompetent patient might have made if he were competent, advances the values of individual autonomy and self-determination.

The "substituted judgement" standard preserves to the extent possible the incompetent's right to self-determination. It preserves the patient's right to make a choice not necessarily in his own best interest, but a choice that is in the best interest of mankind.

Implementing the standard of "substituted judgement" poses some difficult problems. Considering the wide range of treatments available, it is unlikely that the incompetent individual would have expressed, in advance, treatment preferences to cover all possibilities. He or she certainly would not have considered experimental protocols. The proxy decision-maker then has to take into account statements made by the patient in the past, the patient's present circumstances, and the consequences of each treatment.

The situation is particularly difficult when the individual has never been competent. An example might be a patient with Downe's Syndrome. Since the individual has always been of restricted competence, the decision must be based on what a reasonable person with the characteristics of the incompetent patient would have done under similar circumstances. This means that although a "substituted judgement" standard is the preferred method of arriving at a proxy health care decision, in some cases the "best interest" standard must be applied since it is impossible to determine what the individual would have decided if competent. In addition, the surrogate should give permission to participate in a clinical trial only if he or she would be willing to participate in the experiment, were it possible.

Physicians are probably not the best choice to be the proxy decision-maker. Physicians tend to favor treatment and clinical trials over inaction and for this reason are not necessarily in the best position to make a substituted judgement. To have the physician decide first that the patient is incompetent because he or she refused medical treatment and then become the decision-maker seems of inherent dangers. The physician should make proxy treatment decisions only in an emergency when the patient is in imminent danger from lack of treatment.

Hospital administrators are also affected by biases. They may favor treatment if they come from a medical background. If the hospital is in tight financial straits, on the other hand, its officers may favor non-treatment.

Proxy decision-making, for good reason, has fallen for the most part on the family. This is not entirely satisfactory because it may be that the closest blood relative of the patient knows the least about the patient's preferences. It could well be that a long time friend or companion would be in a better position to make a substituted judgement than a member of the family who lived apart from the patient. However, the practice of using family members as decision-makers is so well established it seems unlikely to change any time soon.

It is often difficult to find an appropriate guardian for an institutionalized, incapacited patient. Such a patient may have no family or friends who are qualified and willing to serve. At least one of the States in the United States has a court-appointed ombudsman who reviews proxy decision-making for every incapacitated individual in a nursing home in that state. Sometimes the decision falls on the courts, but the principal role of the court appears to be to serve as an arbiter when the health care providers, the family, and the patient are in conflict.

Institutional review boards (IRB) are an added safeguard for the protection of human research subjects. They must review all proposed biomedical research involving human subjects, approve the initiation of each project, and conduct thereafter a periodic review of the research. The primary responsibility of the IRB is to assure that human subjects are protected adequately, not exposed to unnecessary risks, and provided with sufficient information to give informed consent. This ethical responsibility cannot be completely divorced from a review of the scientific content of the proposed trial to determine if the risks the subject is exposed to are reasonable in relation to anticipated benefits.

Many of these difficult questions of dealing with incompetent patients could be avoided if individuals appointed a surrogate decision-maker prior to becoming incapacitated. In the United States, several kinds of statutes have attempted to address the problem. One kind are the "natural death acts" that have to do with the termination of life support systems. Another kind is the durable power of attorney, which allows individuals to select in advance a proxy health care decision-maker.

Proxy decision-making is founded firmly on many important principles, but the details of determining competence and determining who should serve as the decision-maker are large issues, and I look forward to hearing the discussion. Thank you.

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APPENDIX: RELEVANT GUIDELINES OF THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS

2.07 CLINICAL INVESTIGATION: The following guidelines are intended to aid physicians in fulfilling their ethical responsibilities when they engage in the clinical investigation of new drugs and procedures.

(1) A physician may participate in clinical investigation only to the extent that those activities are a part of a systematic program competently designed, under accepted standards of scientific research, to produce data which are scientifically valid and significant.

(2) In conducting clinical investigation, the investigator should demonstrate the same concern and caution for the welfare, safety, and comfort of the person involved as is required of a physician who is furnishing medical care to a patient independent of any clinical investigation.

(3) In clinical investigation primarily for treatment-

A. The physician must recognize that the physician-patient relationship exists and that professional judgement and skill must be exercised in the best interest of the patient.

B. Voluntary written consent must be obtained from the patient, or from his legally authorized representative if the patient lacks the capacity to consent, following: (a) disclosure that the physician intends to use an investigational drug or experimental procedure, (b) a reasonable explanation of the nature of the drug or procedure to be used, risks to be expected, and possible therapeutic benefits, (c) an offer to answer any inquiries concerning the drug or procedure, and (d) a disclosure of alternative drugs or procedures that may be available.

i. In exceptional circumstances and to the extent that disclosure of information concerning the nature of the drug or experimental procedure or risks would be expected to materially affect the health of the patient and would be detrimental to his best interest, such information may be withheld from the patient. In such circumstances, such information shall be disclosed to a responsible relative or friend of the patient where possible.

ii. Ordinarily, consent should be in writing, except where the physician deems it necessary to rely upon consent in other than written form because of the physical or emotional state of the patient.

iii. Where emergency treatment is necessary, the patient is incapable of giving consent, and no one is available who has authority to act on his behalf, consent is assumed.

(4) In clinical investigation primarily for the accumulation of scientific knowledge-

A. Adequate safeguards must be provided for the welfare, safety, and comfort of the subject. It is fundamental social policy that the advancement of scientific knowledge must always be secondary to primary concern for the individual.

B. Consent, in writing, should be obtained from the subject, or from his legally authorized representative if the subject lacks the capacity to consent, following: (a) a disclosure of the fact that an investigational drug or procedure is to be used, (b) a reasonable explanation of the nature of the procedure to be used and risks to be expected, and (c) an offer to answer any inquiries concerning the drug or procedure.

C. Minors or mentally incompetent persons may be used as subjects only if:

   i. The nature of the investigation is such that mentally competent adults would not be suitable subjects.

   ii. Consent, in writing, is given by a legally authorized representative of the subject under circumstances in which an informed and prudent adult would reasonably be expected to volunteer himself or his child as a subject.

D. No person may be used as a subject against his will.

E. The overuse of institutionalized persons in research is an unfair distribution of research risks. Participation is coercive and not voluntary if the participant is subjected to powerful incentives and persuasion.

2.08 CLINICAL INVESTIGATION: REPLACEMENT OF VITAL HUMAN ORGANS. The following are guidelines, suggested by the Council, in conducting experimental or clinical investigation, such as with mechanical devices or animal organs, for the replacement of human organs that are no longer functional:

(1) Experimental or clinical investigations should be conducted as part of a systematic program competently designed, under accepted standards of scientific research, to produce data which are scientifically valid and significant.

(2) The physicians conducting clinical investigation should demonstrate the same concern and caution for the welfare, safety, and comfort of the persons involved as is required of physicians who are furnishing medical care to patients independent of any clinical investigation.

(3) Voluntary written consent must be obtained from the patient, or from his legally authorized representative if the patient lacks capacity to consent, following (a) disclosure that the physician(s) intend to use an investigational or experimental procedure, (b) a reasonable explanation of the nature of the procedure to be used, risks to be expected, and possible therapeutic benefits, (c) an offer to answer any inquiries concerning the procedure, and (d) a disclosure of alternative procedures, if any, that may be available. Physicians should be completely objective in discussing the details of the procedure to be performed, the pain and discomfort that may be anticipated, known risks and possible hazards, the quality of life to be expected, and particularly the alternatives. Especially, physicians should not use persuasion to obtain consents which otherwise might be forthcoming, nor should expectations be encouraged beyond those which the circumstances reasonable and realistically justify.

(4) In clinical investigation primarily for the accumulation of scientific knowledge, adequate safeguards should be provided for the welfare, safety and comfort of the patient. The medical profession recognizes as fundamental social policy that the advancement of scientific knowledge must always be secondary to primary concern for the individual. The physician must never deny the patient the best possible therapeutic modality in

favor of an experimental treatment which is less likely to succeed.

(5) With the approval of the patient of the patient's lawful representative, physicians should cooperate with the press and media to ensure that medical news concerning the progress of clinical investigation or the patient's condition is available more promptly and more accurately than would be possible without their assistance. On the other hand, the Council does not approve of practices designed to create fanfare, sensationalism to attract media attention, and unwarranted expressions of optimism because of short term progress, even though longer range prognosis is known from the beginning to be precarious. With the approval of the patient or the patient's family, the Council, however, encourages the objective disclosure to the press and media of pertinent information. The situation should not be used for the commercial ends of participating physicians or the institutions involved.

The Council has not evaluated nor does it have sufficient information upon which to base an evaluation as to the extent to which cases involving the use of animal organs and mechanical hearts conform to the above guidelines.

These guidelines are provided to the public, the medical profession, and the scientific community in the belief that they may find them helpful in making their own independent judgements (6).

DISCUSSION: André Boué

Il est généralement admis que les enfants ne doivent jamais participer comme sujets à des recherches que l'on pourrait tout aussi bien effectuer sur des adultes, mais il existe de nombreuses situations où les résultats des recherches sur les adultes ne peuvent pas être extrapolées aux enfants. C'est le cas des processus physiologiques qui, chez le nouveau-né, se produisent lors du passage de la vie intra-utérine à la vie extra-utérine; c'est le cas des processus physiologiques normaux ou pathologiques pendant la croissance ou le développement de différentes fonctions, en particulier le développement mental.

Sur le plan juridique, l'enfant mineur est sous l'autorité des parents pour la protection de sa sécurité et de sa santé.

Toutefois on admet qu'à partir d'un "certain âge" l'enfant mineur peut donner lui-même un "consentement éclairé". Les médecins ont hésité à définir par un chiffre cette notion très subjective de la "maturité", certaines juridictions ont donné une limite, qui varie de 8 à 14 ans. En dessous de cet âge le "consentement éclairé" doit être donné par les parents, mais cette capacité légale a pu être contestée pour ce qui concerne les essais thérapeutiques et la recherche scientifique cognitive.

Trois situations posent des problèmes éthiques:

1) la première situation auquel le médecin pédiatre aura à faire face est l'action thérapeutique simple, en dehors de toute recherche, où le but unique de cette action est la guérison ou, au moins, l'amélioration de la santé de l'enfant.

C'est une situation fréquente en périnatologie où les progrès ûes technologies permettent de maintenir en vie, voire de prolonger la vie, sans pour autant en garantir la qualité. Se pose alors la question de l'abstention thérapeutique, de l'arrêt d'un traitement sans espoir. Ce sont les parents qui supporteront les conséquences affectives et financières des décisions prises. Il peut y avoir des conflits d'intérêt entre l'évaluation de l'avenir prévisible de la santé de l'enfant et le désir des parents qui peuvent soit imposer une thérapeutique sans espoir, soit à l'inverse ne pas tolérer une anomalie mineure.

Une situation conflictuelle peut aussi se présenter lorsqu'un acte thérapeutique indispensable à la survie d'un enfant (transfusion sanguine par exemple) est interdit par la croyance des parents. Dans ce cas le juge des enfants peut arbitrer ce conflit.

2) La deuxième situation concerne les essais thérapeutiques chez les enfants.

Chez le nouveau-né et chez l'enfant les médicaments ont une action et des effet non comparables à ce qui se passe chez l'adulte d'où le caractère indispensable des essais chez les enfants.

a) il peut s'agir d'essais sur des malades ou sur des sujets à risque, essais réalisés dans le cadre de leur traitement donc avec un bénéfice individuel potentiel.

Ces essais devront suivre toutes les règles habituelles des essais médicamenteux chez l'adulte mais devront être précédés des essais chez l'homme adulte et d'essais sur de jeunes animaux en développement.

Dans ce domaine, il ne faut pas oublier d'inclure dans les problèmes éthiques, les essais thérapeutiques de rééducation physique et la psychothérapie.

b) un deuxième chapitre particulier des essais chez l'enfant concerne les études sur les vaccinations et les études diététiques.

Dans le domaine des vaccinations, on doit rappeler que l'efficacité de la vaccination contre la poliomyélite a pu être rapidement démontrée avec un essai avec un groupe placebo d'enfants dont certains ont eu la poliomyélite. Dans ce cas nous avons un exemple d'un bénéfice pour la société car l'efficacité de la vaccination a pu être démontrée rapidement au prix de conséquences graves pour quelques enfants et la décision avait été prise par leurs parents.

Dans le domaine de la diététique on rappelera les polémiques sur l'utilisation des laits industriels au lieu de l'allaitement maternel dans certaines populations défavorisées.

c) Enfin se pose le problème des essais sur des volontaires sains sans bénéfice individuel.

Dans le cas des enfants le "volontariat" est décidé par les parents.

d) Dans ce domaine, il faut aussi parler des investigations génétiques dans les familles. Nous disposons de méthodes permettant de reconnaître dans une famille les sujets porteurs d'une mutation et les sujets sains.

Par exemple dans la Myopathie de Duchenne (Duchenne Muscular Dystrophy), l'Hémophilie, on peut savoir si les soeurs d'un enfant atteint sont porteuses ou non de l'anomalie. Pour cela il faudra faire des prélèvements non seulement sur l'enfant atteint mais aussi sur les enfants sains et parfois l'examen permettra d'offrir un diagnostic prénatal à leur mère ou à leur soeur. Ceci va conduire aux problèmes posés par les registres génétiques et à l'inclusion dans ces registres des informations concernant les enfants et dans un avenir prochain des informations sur des maladies comme la Chorée de Huntington ou la Polykystose rénale (polykistic kidney). A-t-on le droit de faire ces investigations chez des enfants puisqu'il s'agit de maladies qui se déclarent à l'âge adulte et pour lesquelles nous n'avons aucun moyen de prévention?

3) La troisième situation concerne la recherche scientifique pure dans le but d'accroître les conaissances ce qui peut être important pour l'étude du développement normal.

Certaines recherches peuvent se faire sans intervention introduisant une modification dans la physiologie ou le comportement de l'enfant. Le problème éthique pourra être celui de prélèvements de caractère invasif qui pourraient être nocifs, ou simplement douloureux.

Plus important sont les problèmes éthiques liés à des recherches comportant des interventions modifiant la physiologie ou le comportement.

Il peut s'agir de recherches sur des performances physiques, ceci en particulier dans le domaine de la compétition sportive où des entraînements intensifs peuvent nuire à la santé de l'enfant et à son développement. Dans ce cas l'espoir de succès sportifs peut influer sur le "consentement éclairé" de l'enfant mature ou de ses parents.

Il peut s'agir de recherches sur des comportements avec un environnement ou une stimulation inhabituels ou une absence de stimulation, en particulier chez le tout petit enfant, ces interventions pouvant troubler le développement psychique normal de l'enfant. Il peut aussi s'agir de recherches sur des méthodes pédagogiques.

En conclusion:

Il n'est pas possible d'exclure le nouveau-né et l'enfant de certains programmes de recherches, mais l'application des ces programmes doit être entourée de conditions strictes de "non nocivité probable":

- Garantie d'un contrôle médical et familial excellent, de l'expérimentation avec peut-être un "responsable" ou "child guardian" (exemple suédois) des recherches sur l'enfant et une évaluation critique du "consentement éclairé" donné par les parents pour les nouveaux-nés et les enfants très jeunes.

- Extension du "consentement éclairé" aux enfants mineurs "matures" (12 ans et plus??).

La rédaction de ce texte s'est grandement inspirée des rapports contenus dans "Ethique et Pédiatrie" (colloque du Centre International de l'Enfance) édité par Pierre Royer et Jacques Guignard, Flammarion ed. 1982.

Document 8

THE QUESTION OF RESEARCH WITH EMBRYOS AND FETUSES
LA QUESTION DE LA RECHERCHE SUR L'EMBRYON ET LE FOETUS

Albin Eser

Discussion: Gordon Dunstan

Session F / Séance F

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Experiments with Embryos: Legal Aspects in Comparative Perspective

PRESENTATION: Albin Eser

Abstract

1. As is the case with most new technologies, the benefits of modern reproductive medicine also have their price. This can in particular be seen in the sacrifice of embryos for developing and improving IVF-techniques. These developments are also of ethical and legal significance: Unlike the traditional bilateral physician-patient-relationship, artificial insemination has brought in the prospective child as a third party. And if we consider also the possible rights of the embryos which had to be experimented upon before the first test tube baby was born, then the relationship can be considered as fourfold.

2. So far, as exemplified by the present German law, embryos extracorporally produced and not yet implanted are almost without any legal protection. Consequently, it is largely left to medical ethics to give some - more or less clear and enforceable - guidance.

3. In order to overcome this unsatisfactory situation, most countries are about to provide new rules, some even with criminal sanctions. Particular regulations which are under discussion almost everywhere and which will therefore be dealt with in more detail in my oral presentation, are these:

- confining the purposes for which research may be undertaken to improvement of IVF-techniques, or at most to other therapeutic aims, thus excluding experiments with embryos for unspecified or purily biological basic research
- recognition of the embryo as "human life"
- restrictions (if not total prohibition) on non-therapeutic research with embryos
- prohibition of embryo creation specifically for experimental purposes
- prohibition of ectogenesis beyond a certain period
- prohibition of the transfer of embryos after used in experiments
- prohibition of cloning
- prohibition of hybrids and chimera by transgenosis
- restrictions on germinal genic therapy.

4. Further, even where research on the embryo is permitted in principle, there may still be certain requirements and restrictions, such as:

- informed consent of the gamete donors
- approval and/or control by an ethics committee or even a state authority
- confining research to specifically approved centres
- mutual independence of the fertilisation and experimentation teams.

I. Background

As with all new technologies, the exciting developments of modern reproductive medicine also have their prices. (1) This price involves first and foremost the victimization of those embryos that need to be "used up" for the development and investigation of in vitro fertilization (IVF), before any extra-corporally conceived child can successfully be brought into the world.(2)

This statement should not imply any short term moral judgment. Rather it should suggest that in the case of IVF we are dealing with a more complex ethical-legal as well as factually more multidimensional situation than is usual in the traditional doctor-patient relationship. Above and beyond this "bilateral relationship" we must also bring in the welfare of the prospective child. Thus, in effect, we have a problem with "three corners", all of which need to be considered. In addition we need to consider the fate of those embryos that are "used up" in further efforts to improve IVF. To that extent we even have a kind of "four-cornered situation" in which value judgments need to be made: the doctor helps the patient to have a child whose humanity exists at the expense of another embryo (if not many other embryos).
With respect to post-fertilization goals, there are in general three varieties to be distinguished:

- First the case of an embryo, chosen for implantation, upon which examinations or operations are made with the purpose of improving its own chances of development. If the goal of implantation is not achieved, such an embryo can still serve in the discovery of otherwise useful knowledge. Legally, because of its individual and concrete relation to therapy, this case of a "therapeutic trial" ("Heilversuch") would still fall in the category of so-called "therapeutic research".(3)

- Next the case in which an embryo, though originally chosen for implantation, but because of having become "superfluous" by lack of a chance of transfer, becomes a subject of research. This research can have varied goals: improvement of IVF, other medical research, or pure basic research. Because of not promoting the health of the individual embryo in question, such "using up" experiments would fall in the legal category of so-called "human experimentation".

- The latter especially applies to a third category, in which an embryo is designated from the very beginning as a research object, no matter what kind of judgment is envisioned. Without coming to any premature value judgements we might label this category of cases as "experimentally-oriented embryo production".

II. The Present Legal Situation in the Federal Republic of Germany

1. To make it plain from the start: the legal basis for the production of extra-corporally produced, but not implanted, embryos is at present poorly developed. This is definitely so on the level of **federal and state legislation**. Even without going into the highly controversial question of whether, or to what extent, the ovum of a woman, fertilized with the semen of a man, has any claim to constitutional protection, (4) the simple fact is that at this time we do not have a legislative formulation of such a possible constitutional right.

The abortion laws in particular (Section 218-219d StGB = German Penal Code), which are designed to protect unborn life, are not relevant because they presume the existence of "pregnancy". The symbiotic relation between a woman and an embryo that exists in a pregnancy, however, does not exist in the case of a prospective life in a test tube prior to implantation. (5)

At any rate, the application of abortion law is even explicitly precluded since according to Section 219d StGB, interventions which take effect prior to the completion of nidation (i.e. before the egg is fully embedded in the uterus of the mother) do not count as "interruption of pregnancy" in terms of criminal law. (6)

In practice, this means that, under contemporary German law, researchers may do what they please with extra-corporally produced embryos that have not been implanted: they may simply allow them to die, wash them away, or use them for experimental purposes.

2. This image of "outlawry" which seems to be characteristic for the situation of the extracorporal embryo in German law as well as in most other countries, is mitigated, however, by the existence of **ethical self-control** within the research community. This self-regulation includes in particular the "Guidelines for Research on Early Human Embryos", developed by the Scientific Council of the (German) Federal Chamber of Physicians (Bundesarztekammer - BAK Guidelines). (7) Although we are unable to go into greater detail within the scope of this paper, these guidelines in general are based on the following principles:

- Research on human embryos must be carried out within the confines of a formal control procedure (4.1).

- In principle, the production of human embryos solely for research purposes should be forbidden (3.2). This prohibition, however, is not without exceptions, although such exceptions cannot at the present time be delineated in detail.
- Otherwise, research on human embryos - presuming previous animal experiments and high scientific and methodological standards of procedure - should be permissible to the extent that it "has as its goal a direct or indirect clinical benefit in the sense of prophylactic, diagnostic, or therapeutic advances" (3.1).

III. A Reform Draft of the German Federal Ministry of Justice

Despite the fact that proposals for protection of embryos have since been developed in some of the German states - for example, in Bavaria (8) and Rhineland-Platinate (9) - the Federal Ministry of Justice's "Pre-draft of a law for the Protection of Embryos" (Embryonenschutzgesetz - ESchG), (10) made public on April 29, 1986, continues to be of particular interest. It can hardly be expected that this pre-draft (which from now on will be cited as BJM-ESchG) will remain unchanged, especially considering the criticisms of it that have been voiced in various sectors. (11) Nevertheless, because it represents the opinion of the leading ministry in these affairs it carries particular weight both for legislative change and for the development of opinion in this field.

Among its many particular regulations, beginning with a general prohibition against damaging embryos (Section 1), continuing with rules regarding particular IVF-related misuses and unauthorized uses (Sections 2-4), and going on to more gene-technology-related rules (Sections 5-8) that are especially relevant for research on embryos, the following provisions of the draft are of general significance for the researcher:

1. First is the provision related to "damaging of embryos" (1 sect.1 BJM-ESchG), according to which criminal liability would accrue to anyone "who through affecting an embryo or fetus damages the health of the (therefrom originating) human being (that develops from the embryo or fetus)". Even taking into consideration the proviso in Section 1 sect.4 BJM-ESchG, according to which this clause "does not apply to procedures that are designed to bring about an abortion", this offense still covers diagnostic examinations or encroachments on an embryo - whether extra- or intracorporal - which do not lead to the death of the embryo, but rather to post-partum health damages. Thus even a "therapeutic trial" designed to enhance the welfare of the embryo carries a risk of criminal liability, and would need some special justification in order to avoid such liability.

2. The prohibition against production of embryos for research purposes (from which no exceptions are allowed): According to Section 2 sect.1 Nr.1 BJM-ESchG, criminal liability accrues to each person "who fertilizes a human egg cell extracorporally for any purpose other than to transfer it to a woman". It follows that the production of embryos purely for research purposes is forbidden. Furthermore, there are no reservations, so that an exception would only be conceivable in terms of some general legal principle such as "justifying necessity" (Section 34 StGB): thus, for example, a case might arise in which the acute life-threatening condition of a person could only be dealt with by using an embryo in an experiment expected to be fatal to that embryo, and in which no "surplus" embryo was at hand.

3. Further research restrictions may entail from the prohibition against ectogenesis. According to Section 2 sect.1 Nr.2 BJM-ESchG, that person shall be criminally liable "who creates a situation in which a human embryo develops extracorporally beyond that stage in which, in case of natural fertilization, the implantation into the uterus would be completed". This means that - going further than the experimentally-oriented production of embryos mentioned supra 2 - even the extra-corporal cultivation of embryos that were produced for purposes of implantation, may not be extended beyond the natural time period of the so-called nidation. In simple terms this means that, for whatever purposes they were produced, one may not allow embryos to develop in test tubes for longer than 14 days after fertilization. The question naturally follows - a question not dealt with in the BJM-ESchG - about whether one should then simply allow such embryos to die (or even require that they do so) or rather whether freezing, with the possibility of later transfer, should be allowed. Whether or not it was meant to do so by the framers of the draft, a further provision serves as a way of by passing this dilemma:

4. The proviso that, with permission, exceptions may be made to the prohibition against experimentation on "surplus" embryos: According to Section 2 sect.2 BJM-ESchG that person shall also be criminally liable "who, without the permission of the appropriate state authorities, uses extracorporally-produced embryos for experiments with any purpose other than its transfer". This means that although on the one hand research with "surplus" embryos is forbidden in principle, it nevertheless may be permitted by governmental authorities, although no substantive criteria for such permission are given. Without wishing to pass final judgment on this matter it seems that this type of regulation naturally leads to different considerations, depending on one's perspective: The embryo's point of view is that, without any substantive criteria regarding the parameters of such work or any concretizing of the grounds for its being victimized,

it is only protected through the discretion of the respective authorizing agents. The researcher's point of view is that his interests - although possibly contradictory to those of the embryo - are likewise subject to the descretion of public authorities. The result is that one can hardly avoid getting the impression that in these cases the primary concern is less for protection of human life than it is for respect for bureaucratic authority.

5. By contrast, there is the prohibition of experiments on implanted but then aborted embryos and fetuses, which also allows no exceptions. According to Section 3 BJM-ESchG "misuse of embryos and fetuses" is also a criminal act and "whoever, in dealing with an embryo or fetus after abortion 1) keeps it alive artificially or, 2) before its death, performs experiments or procedures that are not conditioned by the aforementioned abortion", shall be criminally liable. This provision also represents further restrictions than are found in the present law, according to which, as has long been the case with duly born life, not only scientific observations but also the taking of tissue samples was tolerated.

With respect to this regulation one cannot help noticing a certain conflict with the existing principle, according to which there is an obligation to keep alive a fetus that is born alive, without consideration for its viability. (12) Therefore Nr.1 and Nr.2 of Section 3 BJM-ESchG should not be viewed as distinct alternatives, but rather they should be understood as together meaning that the artificial prolongation of the life of an aborted embryo is only criminally liable to the extent that it is used for experimental purposes (in the sense of supra no.2).

6. The prohibition against gene transfer into the human germ track, whether through "artificially altering human germ cells" (Section 5 BJM-ESchG) (13) or through "the use of artificially altered germ cells" (Section 6 BJM-ESchG): (14) this permission can curb research at least to the extent that we are dealing with genetic technology procedures that will not be used therapeutically in the foreseeable future, if indeed it were even possible to use them for such purposes.

7. Similarly the prohibition against cloning is particularly directed at researchers (Section 7 BJM-ESchG), (15) since in this field it is also hardly possible to conceive of any therapeutic application.

8. The same holds for the prohibition against development of chimera and hybrids (Section 8 BJM-ESchG). (16)

9. Not the least relevant for research is the understanding of the term embryo. According to Section 9 BJM-ESchG, embryo in the sense of this law is "already the fertilized egg cell from the moment of core fusion, in addition every isolated totipotent cell that is capable of division and of developing to a (human) individual". What this means is there would be no occasion, from the time of the creation of a human germ that under normal circumstances is capable of development, when this entity would be free of legal control. This does not mean that from then on all research possibilities would be precluded. Rather it means that in dealing with a human germ (in contrast to unjoined sperm and egg cells) a researcher may not have unrestricted freedom of action.

IV. International Reform Trends

In order to have reliable and complete picture of international reform tendencies it would be necessary to analyze - in similar fashion as the above analysis of the BJM-ESchG - other laws and policy statements and to explain their relevant research-related consequences. This would not only go beyond the confines of this report, however; it would lead also to a large degree of repetition. Therefore, in the following cursory statements, in which details and nuances must be sacrificed, only some of the basic problem areas will be addressed. Even within these basic problem areas it was in no way possible to take into account the recent wealth of proposed rules and recommendations. Rather I am considering only those that have either legisltative character or - as policy statements of professional bureaucracies or other socio-political organizations - at least a certain official character. To be sure, even this selection cannot claim to be representative.

With these reservations in mind, the following materials were considered from the Federal Republic of Germany:

- The "Rough Draft of a Bavarian Law for the Regulation of Matters Pertaining to Reproductive Medicine" (= BayE-FMedG), (17)
- Rhineland-Palatinate's "Report of the Inter-Ministerial Commission for the Consideration of Questions Related to Bioethics and Reproductive Medicine" (= RhPf-Kommissionsbericht), (18)
- based on the aforementioned report: the "Interim Working Proposal for a State Law about Reproductive Medicine" in Rhineland-Palatinate (= RhPfE=FMed). (19)
- the "Declaration of the Bundesrat Regarding Extracorporal fertilization" (=BR-EntschlieBung), (20)
- the "Social Democratic Proposals Regarding Solutions to the Problem of Infertility and the Application of Genetic Technology in Humans" (= SPD-Vorschlage), (21)

- the report of the working group "In-vitro-fertilization, genome analysis, and genetic therapy" (= Benda-Bericht), (22)
- the report of the enquête-commission on "Chances and Risks of Gene Technology" (=Enquête-Bericht), (23)
- the "Guidelines for Carrying Out In-vitro-fertilization (IVF) and Embryo Transfer (ET) as Methods of Treatment of Human Infertility", developed by the Scientific Council of the Federal Chamber of Physicians (= BAK-Richtlinien I), (24)
- also from the same Council the "Guidelines for Research on Early Human Embryos" (= BAK-Richtlinien II), (25)
- the "Theses Regarding Artificial Insemination of a Working group of the German Federation of Female Jurists" (= DJB-Thesen), (26)
- the resolutions of the 56th German Jurists' Day Berlin 1986 on Artificial Fertilization Among Humans - (= DJT-Beschlusse), (27)
- the "Theses of the German Judges Association Regarding Reproductive Medicine and Human Genetics" (= DRB-Thesen). (28)

From European authorities the following materials are being evaluated:

- the Council of Europe, Parliamentary Assembly, proposed "Recommendation 1046 (1986) (1) on the use of human embryos and fetuses for diagnostic, therapeutic, scientific, industrial, and commercial purposes" (= EC-Recommendation),
- the European Medical Research Councils Advisory Subgroup proposed "Recommendations on Human In Vitro Fertilization and Embryo Transfer" (= EMRC-Recommendations). (29)

From France:

- the parliamentary proposal to the National Assembly entitled "A Proposed Law Relative to the Status of the Conceived Child as well as to Experimentation and Research on the Creation of Human Life (= F-Proposition), (30)
- the proposal of the National Advisory Committee on Ethics for Health and Biological Sciences entitled "Guidelines for the Use of Embryonic Tissue or of Dead Human Fetuses for Therapeutic Diagnostic, or Scientific Uses (= F-CCNE-Tissus), (31)
- the proposal from the same National Ethics Committee entitled "Guidelines for Research on Human Embryos in Vitro, and for Their Use for Medical and Scientific Purposes" (= F-CCNE-Recherches). (32)

From Great Britain:

- the recently-enacted United Kingdom "Surrogacy Arrangements Act 1985" of July 16, 1985 (= GB-Surrogacy Act),
- the statement of the Medical Research Council on "Research related to human fertilization and embryology" (= GB-MRC-Statement), (33)
- the Royal College of Obstetricians and Gynecologists' "Report of the Ethics Committee on In-Vitro-Fertilization and Embryo Replacement and Transfer" (= GB-RCOG), (34)
- the "Report of the Committee of Inquiry into Human Fertilization and Embryology" (=Warnock-Report), (35)
- "The First Report of the Voluntary Licensing Authority for Human In Vitro Fertilization and Embryology" (= GB-VLA). (36)

From Austria:
- Initiative for a Federal Law Concerning Prohibition of Embryo-Manipulation" (= A-Initiative), (37)
- the "Expert Opinion of the Commission of the Austrian Rectors' Conference for In-Vitro-Fertilization" (= A-RK-Gutachten). (38)

From Switzerland:
- The "Medical-Ethical Guidelines for In Vitro Fertilization and Transfer of Embryos for Treatment of Human Infertility", proposed by the Commission for Bioethics Regarding the Handling of Human Germ Cells and Embryos of the Swiss Academy of Medical Sciences (= CH-Akademie-Richtlinien), (39)

From Sweden:
- the report of the Genetics Committee concerning "Genetic Integrity" (= S-Genetikkomitee). (40)

From Australia:
- in Victoria the "Infertility (Medical Procedures Act 1984" (= Victoria-Infertility Act), (41)
- the (national) Draft of a "Human Embryo Experimentation Bill" (= AUS-HEEB), (42)
- the Report of the Senate Select Committee on the Human Embryo Experimentation Bill 1985 (= AUS-Senate Report). (43)

From Canada:
- the Ontario Law Commission's "Report on Human Artificial Reproduction and Related Matters", 1985 (= Ontario Report).

From the USA:

- the proposal of the Judicial Council of the American Medical Association entitled "Bioethical Opinions" (= AMA). (44)

1. It would seem that we could expect many basic policy statements to be advanced regarding the status of the embryo as human life - since this, at least according to widespread opinion, seems consequential, if not even prejudicial, for the feasibility and scope of research on embryos. In fact, however, openly-voiced opinions on this matter are few, with other countries actually showing more restraint in this matter than does the Federal Republic of Germany. Whereas in this country we have comparatively numerous statements of principle claiming the origin of human life to exist at the time of union of sperm and egg, with accompanying demands for protection of this life (45), in other countries we find that similar assurances are more likely to be sporadic. An example is art.1 of France's parliamentary proposition according to which there exists a "legal subject" from the time of the fertilization, whose life is that of a human being and has to be respected as such. Furthermore, we find the same tendencies in the European Council's recommendations according to which human life is developing in a continuous manner from the time of fertilization (Nr.5), and therefore human embryos and fetuses are to be handled in all cases with due respect for human dignity (Nr.10).

Without wishing to denigrate this status problem, we also should avoid over-dramatizing the eventual lack of such express acknowledgements. In other areas the legal recognition of interests is neither necessarily dependent on verbal proclamations but rather, often even in contradictory fashion, follows from the proscription by which violative acts are prohibited. Similarly a matter such as the moral status of the embryo that is so controversial and, more importantly, burdened with so many basic questions about personal and social values, might better be dealt with in less direct fashion. Instead, as already demonstrated by the English Warnock Report, it might be preferable to turn straight away to the question of "how it is right to treat the human embryo". (46)

Vice versa, there are several reasons not to overvalue general proclamations that are meant in favour of the embryo. This is because the protection that is offered is not absolute, but rather relative. There are cases, for example, like the BJM-ESchG, in which it is expressly declared that the respect of human dignity, that should already extend to the embryo, "however, does not preclude differentiations in degree, kind, and extent of the guaranteed protection as compared to later stages of development." (47) Similarly, in other cases, despite recognition of the embryo's human status as a legal subject, particular experiments that do not benefit the embryo are permitted. Therefore the focus of further attention should be directed to the questions of, respectively, whether all encroachments on the fertilized ovum should be forbidden, or to what extent such encroachments should be allowed.

2. As a matter of fact, restrictions (if not total prohibition) on nontherapeutic research on embryos - i.e. research that not even in the form of a "therapeutic trial" (48) might be beneficial for the individual embryo - are found only in isolated instances, and then chiefly in the Federal Republic of Germany. The strongest prohibitions are proposed by the Bavarian Rough Draft, (49) with similar tendencies noticeable in the SPD proposals. (50) The DJT resolutions, (51) however, and the DRB theses, (52) while also directed at prohibitions on research that is not salutary for the individual embryo involved, nevertheless leave open the matter of possible criminal sanctions. The same goes for the Swiss guidelines (53) (which are, however, stricter than those of the BAK II), and the Australian Senate Report. This latter Report, in contrast to generally more permissive Australian antecedents, declares all destructive non-therapeutic research on embryos to be illegal. Furthermore it expressly rejects a differentiation between "surplus" embryos and those produced specifically for research purposes. The Report, however, does not propose to secure its goals through the medium of criminal law, but rather in the form of an administrative license system. (54)
Although similarly restrictive messages also may be found in the European Council Recommendations and in the French bill, these proposals accompany their declarations of fundamental principles with certain allowances. (55)

3. By contrast, the prohibition of embryo creation specifically for experimental purposes, as is found in Section 2 sect.1 Nr.1 BJM-ESchG, is much more widespread. (This is so even beyond those policy positions that would generally forbid any research on embryos in the spirit of supra no.2). this category encompasses two German reports (the majority opinion of the Benda Commission
(56), and the Rhineland-Palatinate Draft Proposal with its call for an administrative fine), (57) the European Council Recommendation, (58) the Austrian Memorandum, (59) and the French Ethics Committee. (60) The BAK Guidelines, although proposing to outlaw such kinds of fertilization "in principle", do not propose to do so absolutely and without possible exceptions. (61)

Furthermore, we should include in this category prohibitions against use of embryos for research purposes in those cases in which embryos, although not expressly produced for research (which would in any case be difficult to prove) are produced in over-supply for transfer purposes. Such a prohibition against production of surplus embryos is seldom articulated in other countries (see, e.g., the Australian Embryo Experimentation) (62) whereas, as in particular in the BAK Guidelines, such production is tolerated in Germany, at least as an exception. (63)

4. Likewise, the prohibition against ectogenesis beyond a certain period is a test case for research on embryos. For, the longer the embryo is allowed to develop in a test tube, the more it becomes available for research purposes, and vice versa. With regard to this matter, international circles are generally in agreement with Section 2 sect.1 Nr.2 BJM-ESchG that the limit should be oriented to the natural nidation period (64). However, we should note on the one hand the Australian Senate Report, which has a rather restrictive (because specially expressed) approach to this matter (65) and, on the other hand, the French Ethics Committee, which finds the determination of a general time limit not to be useful: Instead, similarly to the British College of Obstetricians, (66) it calls for limits that should be developed along with the research designs at the time the research is undertaken. (67)

5. As with ectogenesis, the allowance of, or prohibition against, cryo-conservation of embryos is a measure of the degree to which, in the final analysis, research on embryos should be possible. On the one hand, where - as in the Swiss Guidelines - conservation should be barred even in case of a future use in inducing pregnancy, (68) consequently any "provisory conservation" for research purposes - even if only for a short time - is precluded. On the other hand, where conservation both for implantation and research purposes is admitted - as in Great Britain and Sweden (69) - and furthermore (70), or perhaps instead (71), the time period for conservation is measured liberally, (72) it is possible that an incentive actually would exist for research-oriented "overproduction". Such an immanent dynamic naturally could not be totally prevented even when, as is the prevailing opinion in Germany, conservation should only be used for a short time (2-3 years) (73) and implantation should follow right away or as soon as possible.

However, as soon as this time period is up, and in the case that the anticipated or at least hoped-for transfer did not take place, the question arises of what to do with such an embryo. At the end of the allotted time, rather than simply "washing away" the embryo or, through thawing, allowing it to die, a researcher may then seek to make it "useful" for scientific purposes.

6. With respect to the aforementioned question about permitted research on embryos we are left finally with only those situations in which it has not been precluded by a general prohibition (as supra in category 2) or by prohibition against producing embryos for research (as supra in category 3): in other words, aside from those more general preclusions research is only possible insofar as one is dealing with "surplus" embryos.

Yet, even in this latter case one must differentiate further with respect to the purpose of the research, the major such distinctions being:

- restriction to experiments of a therapeutical nature, that will - as in case of a so-called "therapeutic trial" - involve curative efforts for the benefit of the involved embryo, (74)
- limited expansion as to research that is for the benefit of others, i.e., that may benefit other embryos, people, or generations - while at the same time remaining within the realm of improvement of IVF procedures, (75)
- further expansion to other medicinal purposes, (76)
- whereas the opening of embryo research for any other scientific purpose (i.e., not necessarily medicinal, but also general biological research) has not found any expressed support up to now in official policy statements, such a development, however, should not be judged to be impossible, since there are cases where - as in Section 2 sect.2 BJM-ESchG - the possiblity for obtaining permission to do such research is built into the law without any particular criteria for permission being defined. (77)

In addition one may find, within the previously mentioned permitted limits on embryo research, still further conditions and restrictions, that are partially alternative and partially cumulative in nature:

- Informed consent of the gamete donors, (78)
- Approval and/or control through an Ethics Committee or even a government authority, (79)
- Restriction of embryo research to specifically approved centres, that would be required to meet certain minimum qualifications regarding resources and personnel, (80)
- Separation and mutual independence of the teams that undertake the fertilization work on the one hand and research work on the other, (81)
- Prohibition against commercial uses, (82)
- Time limits on extracorporal cultivation, (83)
- Assurance that embryo research will be subsidiary to animal research. (84)

7. As a further side-effect we should also mention the prohibition against transfer to humans of experimentally-treated

embryos. Whereas in Germany this somehow "consequential prohibition" seems to have been voiced so far only in certain professional circles, (85) in other countries we already find various regulations: either fertilization efforts in scientific laboratories are only permitted for those egg cells for which no intention of transfer exists, (86) or such transfer is forbidden in all cases of embryos that have been exposed to experiments. (87)
To be sure, no matter how modest and able are these concerns about the further transfer of possibly damaged embryos, we are exposing here the real dilemma of research on embryos, a dilemma which may well lead to unanticipated disenchantment with the research: Instead of being able to utilize, for the benefit of an embryo, the results of research originally intended for other uses, and thus become even more involved in therapeutic trials to benefit embryos, forbidding the transfer of embryos that have possibly been damaged through experiments leads rather to their total destruction.

8. Whereas the former considerations dealt with embryo research in general, I should finally also mention some other areas of experimentation that have given rise to the demand for regulation. This is especially so with the prohibition against cloning. Although such manufacture of genetically identical individuals is considered fundamentally undesirable throughout the world, opinions about the urgency and nature of sanctions are varied. Many countries have refrained from taking any official position on this matter; others - e.g. Sweden and probably also the European Council Recommendations - have left undecided the sanctioning of the proposed prohibition. (88) In Victoria, however - similarly as in 7 BJM-ESchG - this action has been criminalized. (89)

9. The equivalent goes for the prohibition against development of hybrids and chimera. Similarly to Section 8 BJM-ESchG such development is prohibited by the European Council's Recommendation and is actually made a criminal offense in Victoria. (90) Obviously these prohibitions cannot forbid every diagnostic test that attaches human to animal germ cells, (91) but rather are meant only to control such core fusion of human germ cells with those of higher-order animals as may lead to actual further development. (92)

10. In the case of genetic transfers into the germ line, although these are also seen as problematic in other countries (93) there is a tendency towards restraint with respect to specific criminal sanctions such as were proposed in Germany by the Benda Commission, (94) and are now proposed in Section 5 BJM-ESchG. This reluctance suggests that one does not want to hamper all possible scientific progress in the area of gene therapy. (95)

V. Towards a Pivotal Politico-Legal Concept of "Moral Status" for the Embryo

Following the above overview of present positions regarding embryo research, an overview that has been more descriptive than evaluative, it would now be useful to undertake a closer evaluation of these positions. Since the space alloted to me, however, will not permit to go into such detail, I would like at least to make a start towards developing a normative position regarding a pivotal point upon which, in the final analysis, all further decisions will depend. I am referring to the "moral status" of the embryo, a matter that is much debated, both nationally and internationally. (96)

Finding a consensus of opinion regarding the moral status of the embryo in the sense of its legal-ethical right to protection is made all the more difficult because such opinion is often - consciously or unconsciously - prejudiced by the desire to give the researcher either more or less freedom of action, depending on one's point of view:

- Those who wish to see research on embryos facilitated, want to deny their human quality from the very start. They base their arguments on the lack of individual personality in the pre-nidation phase of development, or simply on the fact that abortion is not illegal at that phase.

- Those who, on the contrary, find abortion as well as embryo research indefensible, believe their position already founded by assuming that the embryo, from the time of fertilization, has the individuality and personality of a human being and thus is entitled to its own basic legal rights.
  To me, neither of these extreme positions seems to be of particular cogency for the following reasons:

- Even if the embryo has human qualities, it is no more entitled to freedom from all interference than is an individual who has been born. Realistically speaking, even the life of a duly born individual is not treated as "holy" or absolutely entitled to protection. Thus, killing in self-defense (even while mere property interests are being protected), as well as legal killings in war - to say nothing of the death penalty, which is still heavily practiced in some countries - suggest that killing has been justified even in cases of simple material interests or expansionist territorial demands, even without considering whether or not innocent life is at stake. (97) To this extent the much-acclaimed "sanctity" of human life unfortunately is revealed to be a sham, as also can be demonstrated in other places if we look at legal-historical changes regarding protection of human life. (98) In this sense using relative standards in making distinctions about protecting unborn life does not appear to be fundamentally inconceivable. (99)

- On the other hand, however, it would be just as incorrect to conclude that any embryo does not have a right to protection because of the fact that in certain instances abortion is not a criminal offence. Giving priority to the interests of the pregnant woman, as is done in Germany through Section 218a StGB in specific cases of a so-called "indication", (100) does not imply that the embryo is therefore not worthy of protection from the time of its coming into existence. Even taking into consideration Section 219d StGB, according to which interferences before the nidation, i.e. the completion of implantation of the fertilized egg in the uterus, are not considered to be abortions, (101) we cannot conclude simply that we are not dealing with human life prior to the time of nidation. For, like Section 1 German Civil Code which, though connecting the beginning of "legal capability" (Rechtsfahigkeit) with the completion of birth, does not deny the existence of human life prior to that stage, the aforementioned penal norm, too, avoids - very wisely, in my opinion - any definitions of human life and its beginning, and rather limits itself only to describing the boundaries of criminal liability. Similarly the question that is often raised about whether the fertilized egg cell might possess constitutional rights even outside the mother's body, (102) bypasses the heart of the problem. Even without considering the question of when the "personhood" of human life begins, we are at any rate dealing with life that originates from human germ cells and thus is species-specific human in the sense that it is different from any other plant or animal life. And furthermore, when we consider that with a fertilized human egg cell we are dealing with the mere development stage of a human subject that, genetically at least, is completely endowed, that has all its characteristics already enclosed and that only needs to be brought to fruition in order to realize the full potential of a human being, then we can hardly deny all moral status to this "potential subject". (103)

Therefore it would be desirable if the conceptual struggle about whether or not the embryo should be considered a "Mensch", i.e. a "human" in the sense of man or woman, and to what extent this is dependent on its "individuality" or "personality" were abandoned. Likewise, although understandable as an effort to de-emotionalize the issue, the similarly naive (speaking from a normative-theoretical perspective) and rather simplistic efforts to get rid of the basic value problem through terminological "degradation" of the pre-implanted embryo to the status of "pre-embryo" or even to simple "seed" or "germ" should be abandoned. (104) Rather than prejudicing the value questions involved through conceptual-terminological game-playing it would be better to concentrate on the question that is lastly decisive: To what extent does or should a species-specific human (since originating from human gametes) new entity of life - that is, at least genetically, capable of achieving the full potential of a human being - possess sufficient value to make us unwilling to allow for total freedom of choice with respect to maintaining or destroying this life? (105) From this perspective, however, the protection of embryonic human life can neither solely nor decisively depend on being recognized as already possessing and exercising independent basic rights; for, since in other cases the legal order protects some material goods - e.g. culturally valuable collections - even from their owners (Section 304 StGB), there is no reason to suppose that the artificially-produced embryo should be totally kept as an "outlaw". Moreover, just as the claim to protection of animals and plants does not depend upon a corresponding constitutional basis, the claim to protection of the human embryo does not have to stand or fall upon its qualification as "human individual" or "person". For the decisive factor is not the conceptual definition, but rather the amount of esteem that a legal system should accord to a living entity that actually contains within itself the full potential for a human being. Naturally such a claim to protection grows greater to the extent that it can be tied to a constitutional right. lacking this constitutional right, however, does not mean that its worthiness to be protected can be denied. Even ignoring the normative and such related questions about the individuality or personality of an embryo does not mean (and this might easily be misunderstood) that its worthiness to protection should be denied. On the contrary: by making this value-laden and pre-judged matter more relative, we can hope to find a minimal but consensual standard for protection. For it is an undisputed fact of biological knowledge that, even in the case of an extracorporally-produced embryo, we are dealing with a species-specific, genetically determinate human entity. (106)

Drawing the socio-political consequences out of this fact is no longer an empirical matter, but rather a normative evaluation and decision. Without being able to go into great detail here, we can still posit the following with respect to the research on embryos that is at issue here. Since we are acknowledging that a human embryo has to be accrued protection even outside the mother's body, the involvement of this embryo into a research project should not be subject simply to the free discretion of the individual researcher. Rather it should need a specific justification. (107) With respect to this matter three categories of cases (that frequently are not kept separate to a sufficient degree) may be distinguished:

- to the extent that the expected research results can benefit the particular embryo being studied, we are dealing with the essentially permissible case of a "therapeutic trial". (108) For such research the guidelines of the Benda Commission, that allow for the "diagnosis, prevention or treatment of an illness" provide a secure foundation. (109)

- On the other hand, to the extent that such an individual use for the embryo in question is precluded because we are dealing, not with its own welfare, but with a general research project that could benefit other embryos, people, or human generations, we are engaging in what might be considered "non-therapeutical human experimentation". (110) In such a case, however, in which the virtual death of the embryo may be justified only if this result cannot be avoided anyhow and if the degradation of the embryo to object of research is outweighed by defined high ranking medical goals. (111) Even in the case of such a research clause, as conceded by the Benda Commission, (112) one must be aware that in such "instrumental" experiments human life is being sacrificed for other (than their own) purpose: and not only through deleteriously affecting their health but also through the deliberate destruction of life. Such experiments would be inconceivable with born human beings. (113)

- This estrangement of human life finally reaches the stage of total instrumentalization when embryos (for which no plans for implantation exist) are directly and solely produced for research purposes or other uses. If anywhere human life is debased to the point of being purely an object, it is where its destruction is planned at the same time as its creation. Such lack of concern for human dignity would be difficult to justify, even for the most important research purpose. (114) This is even more so when an embryo is produced, and is expected to be used, for commercial purposes. (115)

Furthermore it is important to make clear that the distinction between "surplus" and "specially (for other uses) produced" embryos can become blurred quite easily in practice. For this reason one can appreciate the reasoning behind the Australian Senate Report, which would disallow any such distinctions, and indeed any invasion into an embryo other than for its own sake. (116)

But whatever limits one might wish to set upon embryo research, all we have up to now are mere legal-political postulates. Even if one extended the German Constitutional Court's recognition of right to life of the unborn to the early embryonic life outside the mother's body, (117) we still do not have any operationalization of thisright to protection since our present criminal law, as we showed previously, only comes into effect at the time of nidation. (118) Though it might seem plausible again to protract protection of human life through criminal law to the time of fertilization, as it was understood until the Abortion Reform Law of 1975, such a change is not urgently needed, however. For, since the worthiness of a good or interest to be protected is - though a necessary - not a sufficient condition for criminalizing a violative conduct, it is also essential that criminal sanctions are really needed as well as presumably apt and efficient. (119) Therefore, before resorting to criminal law we would have to consider whether protection of the embryo against uncontrolled experimentation might not be achieved through means other than specifically penal ones. As long as we can presume that research on embryos is being performed by certain identifiable individuals, trained in medicine and bound by professional ethics, it is possible that guidelines such as those suggested by the German Federal Chamber of Physicians (120) would provide an efficient way to avoid abuses in this kind of research. (121) From this standpoint it might also become understandable why the Benda Commission - in contrast to the stricter SPD Proposals (9.4) and especially the criminal sanctions proposed by Section 2 BJM-ESchG (122) - has refrained for the time being from recommending criminalization in this matter.

VI. Permitting Abortions - Forbidding Embryo Research: A Contradiction in Values?

Naturally, no matter what kind of restrictions on embryo research one champions, one soon encounters the argument that such research can be limited only with difficulty when one considers what is so universally tolerated in the case of abortions: "The victimization of single embryos for the use of humankind, what is that compared to - as in Germany - approximately 20,000 abortions each year?" - this and similar kinds of arguments are heard not only unofficially, but also in those official circles that espouse the greatest possible freedom for the conduct of scientific research. Are we upholding contradictory values, then, when we limit embryo research on the one hand, and abortion remains largely unpunished on the other hand? If one is content to deal in simple terms of "comparison of victims", then it seems that "a few embryos more or less" should not matter so much. But is that truly the whole question of "morality" involved in this matter? Without being able fully to develop the implications of these questions, it is worth articulating at least a few thoughts that would tend to counter this type of argument.

First I would like to mention a social-psychological peculiarity, namely that my impression, from many discussions, is that it is preponderantly the conservative anti-abortion researcher who opposes government regulations on research with reference to the much larger incidence of abortion. When, however, one is truly concerned with respect for human life, how can one contemplate further instrumentalization and destruction of unborn life, especially when one considers the potently unsuccessful attempts to regulate abortions? Instead of "as well as" or even "if A, then also B" shouldn't the real key words be "neither - nor"? Or should moral armor in these matters only be easily donned when personal interests are not at stake?

Likewise the previously mentioned "victim arithmetic" is rather superficial. One can imagine, with some cynicism, the outcry that would ensue if one wished to place a value on the life of a newborn by saying that, in view of the large toll of traffic fatalities, war, terrorism, and other such catastrophes, one person more or less doesn't matter. The fact is that human activity is not legitimated by the reality that similar results may obtain from other actions. Thus, for example, killing is not justified by the fact that the victim might have died as a result of an accident or an enemy bullet. Killing must be justified by some kind of legitimate necessity (as in the case of self-defense). Why then should it be totally different with unborn life? In this case also the legitimacy of embryo research cannot simply be based on the fact that other embryos also are being victimized.

In the name of freedom of research, such rationalizations are now actually being advanced. Comparisons are being made between the elevated humanitarian goals of embryo research and the socially-problematic reality of abortions. To the extent that people actually believe that one should refrain from any kinds of restraints on research on the grounds that otherwise one would be adhering to contradictory values, the following should be said. First, a false comparison is being used when one confronts the factual abuse of the abortion law with a presumable high ethos of the researcher. Wouldn't it be fairer first to compare the state of law in both areas? According to present law the decision to have an abortion is conditional, and may not be made freely by the pregnant woman, whereas experiments on extracorporal embryos are totally unregulated at present and are not subject to any conditions. Therefore we can only hope, but not guarantee that lethal experiments with embryos are limited to really high-ranking medical goals. If criteria for research on embryos were developed, then we would have nothing more than a situation comparable to the one in which permission for an abortion is legally regulated: just as the pregnant woman and her doctor have to justify their actions, the same would be expected of the embryo researcher. Then, even without taking into consideration the fact that the pregnant woman is involved to a much greater extent on a personal level than is the researcher, we could validly begin to talk about contradictory values when regulations regarding permission to do embryo research and those permitting abortions deliberately were made to lack equivalence. Thus, for example, there could be the extreme case of, on the one hand, prohibition of embryo research without exception and, on the other hand, unregulated freedom to abort. It would be the same if, despite close similarities in law between these two types of cases, as a matter of fact abortion in practice would be totally unrestricted, whereas the embryo researcher would run the risk of serious sanctions.

It would be difficult, however, to maintain that such discrimination against the embryo researcher is envisioned in the presently-proposed regulation. Without, on the one hand, trivializing the massive number of abortions or, on the other hand, wishing to cast doubt on the assuredly high ethics of our researchers, it seems that, with regard to this question, too, sobermindedness without ideological prejudice would be the proper posture to take.

Footnotes

1) For a general discussion of this ambivalence within modern biotechnology, as well as of the conflicting interests within this field that must be considered see A. ESER, Gentechnologie und Recht: Der Mensch als Objekt von Forschung und Technik, in H. DAEUBLER-GMELIN/W. ADLERSTEIN (eds.), Menschengerecht, 1986, pp. 149-172.

2) Now as always I use such terms as "using up" ("verbrauchende", "consuming") experiments, which have become part of the professional idiom in this field, with the greatest reluctance. Cf. also the critique of H.-B. WUERMELING, Verbrauchende Experimente mit menschlichen Embryonen, in: Muenchener Medizinische Wochenschrift (MMW) 1983, pp. 1189-1191.

3) Contrary to a common understanding among physicians, we are no longer concerned here with the category of "therapeutic treatment", but rather with an experimental trial. Therefore, we are basically dealing with research uses, even if one calls this effort "therapeutic research" designed to foster the welfare of the embryo in the sense of the Tokyo-Helsinki Declaration. For a closer analysis of this distinction between "therapeutic treatment" and "therapeutic trial", as well as the attendant category of "human experimentation" (non-therapeutic research), see A. ESER, Das Humanexperiment, in W. STREE et al. (eds), Gedaechtnisschrift fuer H. Schroeder, 1978, pp. 191-215, esp. p. 198 ss.

4) Cf. - in addition to my report mentioned above in footnote 1 p. 152 s., 162 ss. - namely E. BENDA, Humangenetik und Recht - eine Zwischenbilanz, in: Neue Juristische Wochenschrift (NJW) 1985, pp. 1730-1734; H. HOFMANN, Biotechnik, Gentherapie, Genmanipulation - Wissenschaft in rechtsfreiem Raum?, in: Juristenzeitung (JZ), 1986, pp. 253-260; M. PAP, Die Wuerde des menschlichen Lebens in Vitro, in: Medizinrecht (MedR) 1986, pp. 229-236; E.H. RIEDEL, Gentechnologie und Embryonenschutz als Verfassungs- und Regelungs- problem, in: Europaeische Grundrechtszeitchrift (EuGRZ) 1986, pp. 469-478; Ch. STARCK, Die kuenstliche Befruchtung beim Menschen - Zulaessigkeit und zivilrechtliche Folgen, 1. Teilgutachten, Verfassungsrechtliche Probleme, in: Verhandlungen des 56. Deutschen Juristentages Berlin 1986, esp. at A p. 13 ss.

5) Cf. H.-G. KOCH, "Medizinisch unterstuetzte Fortpflanzung" beim Menschen - Handlungsleitung durch Strafrecht?, MedR 1986, pp. 259-265, esp. p. 263.

6) Closer to this A. ESER, in: SCHOENKE/SCHROEDER, Kommentar zum Strafgesetzbuch, 22.ed. 1985, prenote 26 s. to Section 218 as well as Section 219d notes 2 ss.

7) "Richtlinien zur Forschung an fruehen menschlichen Embryonen", published in: Deutsches Aerzteblatt (DAEBl) 1985, pp. 3757-3764.

8) See infra note 17.

9) See infra note 19.

10) "Diskussionsentwurf eines Gesetzes zum Schutz von Embryonen" des Bundesministeriums der Justiz, the full text of which is published (though without the official opinion) by E. DEUTSCH, Der Diskussionsentwurf eines Gesetzes zum Schutz von Embryonen (ESchG), in: Zeitschrift fuer Rechtspolitik (ZRP) 1986, pp. 242-243, as well as in MPG-Spiegel (infra note 11); cf. also R. HESS, Rechtsprobleme der In-vitro-Fertilisation und der Leihmutterschaft, MedR 1986, pp. 240-244.

11) As in the (as yet unpublished) policy position of the German Federal Chamber of Physicians (Bundesaerztekammer), as well as in the memoranda of the German Research Foundation (DFG-Press-release of March 9, 1987) and the Max Planck Society (in: MPG-Spiegel 3/87 pp. 33-39).

12) Cf. ESER in Schoenke/Schroeder (supra note 6) prenotes 13 ss. to Section 211.

13) According to Section 5 BJM-ESchG it shall be an offence to "artificially change the genetic information of a human germ track cell without having insured that it will not be developed further into either a germ cell or a human being".

14) According to Section 6 BJM-ESchG it shall be an offence "to use, for fertilization purposes, an egg or sperm cell that has undergone artificial genetic change".

15) According to Section 8 BJM-ESchG it shall be an offence: (sect.1) "to produce and develop further a human embryo that has the same genetic information as another embryo, or as a fetus, a living person, or a dead person;" (sect.2) "to transfer an embryo such as was described in sect.1 into the body of a woman".

16) According to Section 8 BJM-ESchG it shall be an offence (sect.1) to "1. unite to a cell group, that is capable of development, embryos with different genetic information, using at least one human embryo, or 2. through fertilizing an animal's egg cell with the semen of a human man, produce an embryo that is capable of development; and further (sect.2) "to transfer such embryos as described in no.1 or 2 into the body of a woman". - Cf. however also below at IV.9 regarding feasible forms of interspecies-interactions.

17) "Rohentwurf eines Bayerischen Gesetzes zur Regelung von Fragen der Fortpflanzungsmedizin" (= BayE-FMedG), approved July 29, 1986 by the Bavarian Council of Ministers, printed in: H.SEESING (ed.), Technologisher Fortschritt und menschliches Leben. Die Menschenwuerde als MaB*stab der Rechtspolitik, series "Gentechnologie - Chancen und Risiken", vol.11, 1987, pp. 99-118, esp. pp. 113-118.

18) Rheinland-pfaelzischer "Bericht der interministeriellen Kommission zur Aufarbeitung von Fragen der Bioethik-Fortpflanzungsmedizin" (= RhPf-Kommissionsbericht) of 18.3.1986, also printed in SEESING, (supra n.17) pp. 119-136.

19) "Vorlaeufiger Arbeitsentwurf eines Landesgesetzes ueber Fortpflanzungsmedizin" von Rheinland-Pfalz (= RhPfE-FMed) of 14.10.1986, also printed in SEESING (supra n.17), pp. 137-141.

20) "EntschlieB*ung des Bundesrates zur extrakorporalen Befruchtung" (= BR-EntschlieB*ung) of 16.5.1986, BR-Drucksache 210/86.

21) "Sozialdemokratische Vorschlaege zur Loesung von Problemen der Unfruchtbarkeit und der Anwendung gentechnologischer Methoden

beim Menschen" (= SPD-Vorschlaege), printed in: H.DAEUBLER-GMELIN (ed.), Forschungs-Objekt Mensch: Zwischen Hilfe und Manipulation. series "Gentechnologie - Chancen und Risiken", vol.7, 1986, pp. 1-16.

22) The report of this - after its chairman, a former president of the Federal Constitutional Court - so-called BENDA-commission, that was set up in May, 1984 by the Federal Minister for Research and Technology in conjunction with the Federal Minister for Justice, and that published its recommendations on October 25, 1985 in hectographic form, has since been published in book form, in the series "Gentechnologie - Chancen and Risiken", vol.6: In-vitro-Fertilisation, Genomanalyse und Gentherapie. Bericht der gemeinsamen Arbeitsgruppe des Bundesministers fuer Forschung und Technologie und des Bundesministers der Justiz, 1985. In order to facilitate access to these two published forms of this so-called "Benda-Bericht", I will refer to the sections of the outline rather than to page numbers.

23) Bericht der Enquête-Kommission "Chancen und Risiken der Gentechnologie" (= Enquête-Bericht), Bundestags-Drucksache 10/6775 of 6.1.1987; also in book form published by W.-M/ CATENHUSEN/H. NEUMEISTER (eds.), Enquêtekommission des Deutschen Bundestages - Chancen und Risiken der Gentechnologie. Dokumentation des Berichts an den Bundestag, series "Gentechnolgie - Chancen und Risiken", vol.12, 1987. Here the figures are also referred to.

24) "Richtlinien zur Durchfuehrung von In-vitro-Fertilisation (IVF) und Embryotransfer (ET) als Behandlungsmethode der menschlichen Sterilitaet" (= BAEK-Richtlinien I), published in DAEB1 1985, pp. 1691-1698.

25) "Richtlinien zur Forschung an fruehen menschlichen Embryonen" (= BAEK-Richtlinien II), printed in DAEB1 1985, pp. 3757-3764.

26) "Thesen einer Arbeitsgruppe des Deutschen Juristinnenbundes zu kuenstlichen Befruchtungen" (= DJB-Thesen), published in JZ 1986, pp. 777-778.

27) "Beschluesse des 56. Deutschen Juristentages Berlin 1986, I. Abteilung Zivilrecht: Die kuenstliche Befruchtung beim Menschen - Zulaessigkeit und zivilrechtliche Folgen" (= DJT-Beschluesse), published in NJW 1986, pp. 3069-3070.

28) "Thesen des Deutschen Richterbundes zur Fortpflanzungsmedizin und zur Humangenetik - BeschluB* der Bundesvertreterversammlung" (= DRB-Thesen), published in: Deutsche Richterzeitung (DRiZ) 1986, pp. 229-230.

29) "Recommendations on Human In Vitro Fertilisation and Embryo Transfer" (= EMRC-Recommendations), published in: The Lancet 1983, p. 1187.

30) "Proposition de loi relative au statut de l'enfant conçu ainsi qu-aux expérimentations et recherches concernant la création de la vie humaine" (= F-Proposition), Assemblé Nationale No. 2158 of 18.4.1984.

31) "Avis sur les prelevements de tissus d'embryons ou de foetus humaines morts, a des fins therapeutiques, diagnostiques et scientifiques" by the Comité Consultatif National d'Ethique pour les sciences de la vie et de la santé of April 1984 (= F-CCNE-Tissus).

32) "Avis relatif aux recherches sur les embryons humains in vitro et a leur utilisation a des fins medicales et scientifiques" by the Comité Consultatif National d"Ethique pour les sciences de la vie et de la santé of December 15, 1985 (F-CCNE-Recherches).

33) Published in: British Medical Journal 285 (1984), p. 1480.

34) Proposal of March, 1984.

35) Issued by Department of Health & Social Security, London 1984.

36) Published in April 1986.

37) "Initiativantrag fuer ein Bundesgesetz ueber das Verbot der Embryo-Manipulation" (A-Initiative), Representatives Dr. Maria Hosp et al; II-3306 of the Appendix to the Stenographic Protocol of the National Council, 16th Legislative Period, Nr.156/A of September 25, 1985.

38) "Gutachten der Kommission der Oesterreichischen Rektorenkonferenz fuer In-vitro-Fertilisation" (= A-RK-Gutachten), prepared in June 1986.

39) "Medizinisch-ethische Richtlinien fuer die In-vitro-Fertilisation und den Embryonentransfer zur Behandlung der menschlichen Infertilitat" der Schweizerischen Akademie der medizinischen Wissenschaften (= CH-Akademie-Richtlinien), published in: Schweizer Aerztezeitung 1985, p. 1127 ss., and meanwhile declared legally binding in the Cantons of Genf and Waadt (Schweizer Juristen-Zeitung 1986, pp. 271-272).

40) Gentisk integritet. Betankande av Gentikkommittén. SOU 1984:88, Stockholm, 1984. This committee was set up by the Social Ministry on October 29, 1981. In 1983 it released an

interim report, and in November, 1984 the final report was released.

41) Victoria No.10163. Cf. most recently also P. KASIMBA, Experiments on Embryos - Permissions and Prohibitions Under the Infertility (Medical Procedures) Act 1984 (Vic.), in: the Australian Law Journal 60 (1986) pp. 675-679.

42) "A bill for an act to prohibit experiments involving the use of human embryos created by in-vitro-fertilization" of 1985.

43) Published as: Human Embryo Experimentation In Australia, Canberra 1986.

44) For the situation in the USA of. also N. SCHMID, Strafrechtliche Schranken gegen Manipulation mit ungeborenem Leben? Eine Problemuebersicht und Hinweise auf amerikanische Loesungsansaetze, in: Festschrift fuer C. HEGNAUER, 1986, pp. 433-451.

45) Thus - beyond Section 9 BJM-ESchG, mentioned supra at III.9 - especially in the BR-EntschlieB*ung IV.1, the DRB-Thesen I, the DJT-Beschluessen VII.1, VII.2, the BAEK-Richtlinien II Appendix to 1; RhPf-Kommissionsbericht Thesis II.

46) Cf. Warnock-Report p. 60; cf. also the Australian AUS-Senate-Report Nr.3.22, 3.23: Without giving the embryo the status of a person in either the ethical or the legal sense, the Committee nevertheless adopts the premise that the dignity that attaches to the embryo upon fertilization demands protection against destructive non-therapeutic experiments.

47) Cf. the introduction to the BJM-ESchG p. 8.

48) Cf. supra to note 3.

49) Cf. Art.5 in connection with Art.6 I Nr.5 BayE-FMedG.

50) Cf. SPD-Vorschlage 9.4.

51) Cf. esp. DJT-Beschluesse VII.3-7.

52) Cf. DRB-Thesen II., IV.1., IV.3.

53) CH-Akademie-Richtlinien Nr.7.

54) Cf. AUS-Senate Report esp. p. XIV ss., p. 29 ss.

55) Cf. EC-Recommendation Nr.14.A (i.e. prohibition against experimentation on living human embryos, whether viable or not)

on the one hand and, on the other hand, Nr.15 (where in the context of scientific research on embryos the need for balance between freedom of research, respect for human rights, and other human rights considerations are discussed). See also the F-Proposition, according to which scientific research on embryos (forbidden in Article 5) may still be carried on (according to Article 8) with special permission: In other words, such research is not totally precluded.

56) Cf. Benda-Bericht A.2.4.1; also RhPf-Kommissionsbericht These III. and IV.4.a.; DJB-These I; DRB-These II; DJT-Beschluesse VII.3.

57) Sections 1 II, 8 I Nr.1 RhPfE-FMedG.

58) EC-Recommendation Nr.14.III.

59) A-RK-Gutachten p. 34, 48 ss.

60) Cf. F-CCNE-Recherches III.B.b.

61) BAEK-Richtlinien II Commentary to 3.2; also the majority opinion of the Warnock Commission (cf. Warnock-Report p. 69), which, in putting time limits on research, includes such embryos as were produced expressly for research purposes.

62) Cf. AUS-HEEB Art.5(3). In the same vein also A-RK-Gutachten p. 34 s. as well as the F-CCNE-Recherches III.B.b.

63) Cf. BAEK-Richtlinien II Nr.4.1.

64) Cf. supra to III.3. the Benda-Bericht (4.2.1.1) and the EMRC-Recommendations would allow cultivation only to the time of early cell divisions. On the other hand, Art.5 II Nr.2 BayE-FMedG is oriented towards the time of nidation which, as in the BAEK-Richtlinien II (3.3.2), is considered to be completed at the 14th day after fertilization. Likewise the EC-Recommendations (14.A.IV.), the Warnock-Report (p. 69), the GB-MRC-Guidelines (IV), the GB-VLA (Nr.7), and the A-RK-Gutachten p. 40, 50, restrict the time limit, as does the S-Genetikkomitee with the reservation that the time of cryo-conservation be subtracted.

65) Cf. AUS-Senate-Report p. 29.

66) Cf. GB-RCOG V.12, 13.

67) Cf. F-CCNE-Recherches, III.B.b.1, that, however, nevertheless takes a definitive stand against cultivation beyond the

nidation stage, while determining this stage at the 7th day after fertilization.

68) CH-Akademie-Richlinien Nr.6. Although not clearly articulated in the same sense, Art.4, 5 of the BayE-FMedG also appear to set restrictions according to this standard.

69) Cf. GB-VLA Guidelines 7, 8 as well as S-Gentikkomitee. On the other side is the report of the Swedish IVF Committee (Barn Genom Befruktuing Utanfor MM. Betankande av inseminationsutredningen. SOU 1985:05, Stockholm 1985), that would only allow cryo-conservation for the improvement of an on-going infertilization therapy.

70) Thus, GB-VLA-Guidelines 8.

71) Thus, GB-Warnock-Report p. 10.

72) Thus, according to the aforementioned British guidelines, up to 10 years, whereas the Swedish Genetics Committee has proposed (without, however, fixing an exact time limit) that the same conservation period be allowed for research uses as is allowed for implantations.

73) Thus the Benda-Bericht A.2.5.1.2; cf. also Section 6 IV RhPfE-FMedG, DRB-These III. Furthermore cf. Art.4 F-Proposition, regarding the possibility of special approval, but exclusively in the interest of the child or mother, and admittedly without setting a deadline.

74) Thus specifically the AUS-Senate Report 2.31, 2.35, whereas neither Bavaria's nor Rhineland Palatinate's draft takes such a clear stand. Also the EC-Recommendations as well as the F-Proposition, despite first appearances, also allow certain exceptions (cf. supra to IV.2) thus the EC-Recommendations distinguish between general prohibition of "experimenting" on living embryos and prohibition restricted to research on viable embryos (Nr.14 A IV Nr.10 and 11).

75) Thus also the F-CCNE-Recherches III.B.b that, while in general allowing research for medically-relevant purposes, nevertheless only mentions improvment of IVF techniques in the cited examples.

76) Thus Benda-Bericht 2.4.1.2; BAEK-Richtlinie II.3.1.2;; cf. also GB-MRC-Guidelines (i), that deal with differential diagnosis and treatment of inherited diseases. Likewise the GB-VLA Guidelines 1 and 3, that speak of "scientifically sound" research and give as example - beside the improvement of IVF techniques and contraceptive measures - the diagnosis and

treatment of genetic disorders. A similar situation is found in F-Proposition Art.5.1, 5.2, and F-CCNE-Tissu I.1 as well as the Austrian A-RK-Gutachten, p. 37 ss. More extreme is the Warnock Report, p. 71, which holds that in exceptional cases the testing of pharmaceuticals on embryos should be allowed.

77) Cf. supra III.4.

78) Thus specifically Art.5 II Nr.5 BayE-FMedG; Benda-Bericht 2.4.2.1.1.; BAEK-Richtlinien I Nr.3.4.4 and Richtlinien II Nr.3.3.1.; RhPf-Kommissionsbericht These VI; A-RK-Gutachten p 35; F-CCNE-Recherches III.B.a.1. lin.2 und III.B.b.1, that sets graduated degree of information according to risk and potential usefulness. Cf. further EC-Recommendations Appendix B.IV.d.; GB-MRC-Guidelines (ii), (iii), GB-VLA-Recommendations Nr.5 and 6; Warnock-Report p. 66; CH-Akademie-Richtlinien Nr.9; S-Genetikkomitee.

79) Thus Benda-bericht 4.2.2.1; BAEK-Richtlinien II Nr.4.2-4.3; RhPf-Kommissionsbericht to these VI; EC-Recommendations 14.A.VII; A-RK-Gutachten p. 42, F-CCNE-Tissus II.a.; F-CCNE-Recherches III.B.a.1. lin.3, III.B.a.2 lin. 3 and III.B.b.4., that call for the consent of the Comité Consultatif National d"Ethique when the research is for other purposes, but that allow for control through local ethics committees in other cases; Warnock-Report p. 75 ss.; GB-VLA Guidelines 5, 12, 13a, according to which the VLA sees itself to be a voluntary and non-government authority that would, however, allow for the participation of local ethics committees. See also A-Initiative Art.1 Section 3; S-Genetikkomitee and AMAS 2.08 (6).

80) SPD-Vorschlaege 9.1; RhPf-Kommissionsbericht IV.1. to These I; EC-Recommendations 14.A.VI and Appendix B.VI.b.; A-RK-Gutachten p. 30; F-CCNE-Tissus II.a.; F-CCNE-Recherches III.B.a.1. lin.3; GB-VLA-Guidelines Nr.12.

81) So expressly F-CCNE-Tissus II.a.; F-CCNE-Recherches III.B.b.3, IV.

82) BAEK-Richtlinien I. Nr.4.4; DJT-Beschluesse VII.8.; EC-Recommendations Appendix B.IV.e. Explicitly criminal sanctions are envisioned in: RhPf-FMedG Section 8 III; F-Proposition Art.9; A-Initiative Art.II Section 4 and SPD-Vorschlaege 9.4.

83) As set out above in 4.

84) Benda-Bericht 4.2.1.1.; BAEK-Richtlinien II Nr.3.1.1.; RhPf-Kommissionsbericht These VI; F-CCNE-Tissus III. B.a.2. line 1 and III.B.b.1 line 2; GB-VLA Guidelines Nr.2; AMA 2.08 (2).

85) Thus in a (not-yet-published) policy position of the German Society for the Study of Fertility and Sterility with regard to "Moral-Ethical Boundaries in Dealing with Human Embryos".

86) EMRC-Recommendations 3; AMA 2.11.

87) GB-VLA-Guidelines Nr.4; Warnock-Report p. 66; S-Gentikkomitee.

88) Cf. S-Gentik-Komitee C, EC-Recommendation Nr.14 A.iv.

89) Cf. Victoria Infertility Act sec.6; in the same vein see Benda-Bericht A.2.6.1.1.1; further the SPD-Vorschlaege Nr.10.2a, Enquête-Bericht C.6.3.3.7., the DRB-Thesen VII, and for Austria A-RK=Gutachten p. 40, 50.

90) Cf. EC-Recommendation Nr.14 A.iv, Victoria Infertility Act sec.6; likewise Benda-Bericht A.2.6.2.2.1., SPD-Vorschlaege 10.2a, DRB-Thesen VII., Enquête-Bericht C.6.3.3.7. Similarly in Austria for a penal prohibition A-RK-Gutachten p. 40 s., 50.

91) Cf. GB-MRC-Guidelines (vi).

92) Cf. ESER (supra note 1) p. 168 s.; id., Strafrechtliche Schutzaspekte im Bereich der Humangenetik, in: V. BRAUN/D. MIETH/K. STEIGLEDER (eds.), Ethische und rechtiche Fragen der Gentechnologie und der Reproduktionsmedizin, series "Gentechnolgie - Chancen und Risiken", vol.13, 1987, pp. 120-149, at 145 s.

93) Cf. F-CCNE-Tissus III.D as well as the recommendations of the 2. International Conference on Bioethics in Rambouillet (April 1985), in Cesta (ed.), International Conference on Bioethics, Paris 1985, pp. 319-352 (at I.2); also A. ESER, Gentechnolgie - Rechtspolitische Aspekte aus internationaler Sicht, in: Gentechnologie und Verantwortung (Max-Planck-Gesellschaft/Berichte und Mitteilungen 3/85, Muenchen), pp. 53-64.

94) Benda-Bericht A.4.2., as well as Enquête-Bericht C.6.3.3.7.

95) Cf. H. HOFMANN, Biotechnik, Gentherapie, Genmanipulation - Wissenschaft im rechtsfreien Raum?, in JZ 1986, pp. 253-260, at p. 260, and D. STERNBERG-LIEBEN, Gentherapie und Strafrecht, in: Juristische Schulung (JuS) 1986, pp. 673-680, at p. 679, who expressly take a stand against criminalization; instead they recommend administrative regulation. In contrast the SPD-Vorschlaege 10.2b and DRB-Thesen VIII presume a general prohibition, but leave open the question of sanctions.

96) Cf. ESER on the Rambouillet-Empfehlungen (supra n.93); furthermore the introduction to F-CCNE-Recherches as well as AUS-Senate Report pp. 25 s.

97) On the same line, holding that the classification as "human life" or the accruement of "human dignity" do not say anything definitive about the possibility of permitting interventions, see also R. HERZOG, Die Menschenwuerde als Masstab der Rechtspolitik, in Seesing (supra n.17), pp. 23-32, at p. 27 s.

98) Cf. A. ESER, "Sanctity" and "Quality" of Life in a Historical-Comparative View, in: S.E. WALLACE/A. ESER, Suicide and Euthanasia - The Rights of Personhood, 1981, pp. 99-105, further A. ESER, Freiheit zum Sterben - Kein Recht auf Toetung, JZ 1986, p. 786-795, esp. p. 789 s.

99) In the same vein BJM-ESchG Introduction p. 8 as well as A-RK-Gutaechten p. 32 f. Cf. also HOFMANN, JZ 1986, p. 259.

100) For more details see A. ESER, Reform of German Abortion law, in: 34 Am.J.of Compar.Law (1986) pp. 369-383, at 374 ss.

101) Cf. supra to II.1.

102) IN confirmation, see specifically DJT-Beschluesse VII.2, Ch. STARCK, Gutachten A zum 56. Deutschen Juristentag 1986, p. 15 ss., These 5; cf., i.a. also E. BENDA, NJW 1985, pp. 1730-1734; W. GRAF VITZTHUM, Gentechnologie und Menschenwuerde, MedR 1985, pp. 249-257; for reservations, see HOFMANN, JZ 1986, p. 259.

103) In the same vein, see Benda-Bericht A.1.3., BR-EntschlieB*ung IV.1, DJT-Beschluesse VII.1, DRB-Thesen I.

104) In this context is also HERZOG's lack of understanding of the "grimness with which the beginning of life is debated on all sides" (loc.cit. supra n.97 at p. 28).

105) This is the context in which the portion of the Warnock Report given supra at note 46 can be understood. Similarly, see AUS-Senate Report p. 25 ss., as well as A-RK-Gutachten p. 32 ss.

106) As a result the definition of "species-specific" human life found in Appendix B.IV of the Benda Bericht has not been contested even by natural science circles.

107) Such a requirement for justification may seem strange in view of the researcher's constitutionally-guaranteed right to freedom of research (as according to Art.5 in the German Basic Law). It is explained, however by the fact that this freedom

has limits related to interests that themselves have some claim to legal protection. For a closer analysis, see A. ESER, Recht und Humangenetik, in: W.SCHLOOT (ed.), Moeglichkeiten und Grenzen der Humangenetik, 1984, pp. 185-209, esp. p. 190 ss.

108) Cf. supra I at note 3.

109) Benda-Bericht A.2.4.1; likewise DJT-Beschluesse VII.7.

110) Here also cf. supra I at note 3.

111) Even this rather cautious approach, however, opposed by the DRB-Thesen IV.1, and also the DJT-Beschluesse VII.6. In the same vein most recently also the AUS-Senate Report, p. XV, 29 ss., according to which the capacity even to differentiate between "spare" and "specially created" embryos is disputed.

112) Benda-Bericht A.2.4.1.

113) For a closer analysis, see ESER in Schroeder-Gedaechtnisschrift (supra, note 3) p. 210 ss.

114) Similarly opposing are the BR-EntschlieB*ung IV.2, 3, the DJT-Beschluesse VII.3, and the DRB-Thesen II. Even the A-RK-Gutachten, that generally tends to hold back in recommending criminalization, in this respect also takes a limited stand in favor of criminalization of production of embryos for research purposes (pp. 48 ss.).

115) Cf. DJT-Beschluesse VII.8.

116) Cf. supra at IV.2.

117) Cf. Benda-Bericht A.1.3 to BVerfGE (= Entscheidungen des Bundesverfassungsgerichts) vol. 39 (1975) p.1, 37 as well as BJM-ESchG Introduction p. 7 s.

118) Cf. above II.1.

119) For a closer analysis of these three basic requirements of criminalization - i.e. a legal interest that deserves and needs protection by criminal law and that is apt to be protected by criminal sanctions (Schutzwuerdigkeit, Strafbeduerftigkeit, and Straftauglichkeit) - see ESER, in: BRAUN/MIETH/STEIGLEDER (supra n.92) at 123 ss.

124) Cf. esp. BAEK-Richtlinien I to 4.3 in combination with BAEK-Richtlinien II.

125) In this respect, however, one should take note (as in fact was done by KOCH MedR 1986, p. 264) of the fact that as "offenders" not only physicians but also biologists are meant. These latter are not necessarily bound by the kind of professional regulation that exists in physicians' groups. So long as access to embryos is in the hands of controllable and controlling physicians and no highly serious misuse needs to be of concern, however, one should now give peer review by ethical committees at least a chance to be tried.

122) Cf. supra at III.2-4.

DISCUSSION: Gordon Dunstan

First may I express my deep appreciation of Professor Eser's presentation of his case, its thoroughness, its comprehensiveness and its clarity. It would be folly for me to try to argue point by point against his most impressive analysis of the moral status of the human embryo, particularly because my German was not good enough to read his paper before I came. I had to rely on the summary when I prepared my original thoughts. It would, I say, be presumptuous for me to try to analyse that case in detail on simply having heard his presentation. However, I will reflect a little upon a few things.

First, I should say that I am a member of the Voluntary Licensing Authority which was set up by our Medical Research Council and Royal College of Obstetricians and Gynaecologists to implement the recommendations of the Warnock Committee. I emphasize that this regulation, which is now entering its third year, acts entirely by consent. It has no coercive authority, no one is bound to obey, and yet the thirty centres practicing _in vitro_ fertilization and GIFT (gamete intra-fallopian transfer) techniques all accept our jurisdiction and our guidelines. This is an interim measure until the government can legislate. We hope that by doing this voluntarily and on a consensual basis we are gaining enough experience to give the government good ground on which to legislate. A law built on workable experience might well be a better law than one thought up in the appropriate government department without the test of experience.

I would recall, if I may, a point made earlier, that we cover in our supervision both genuine research with embryos, and indeed with oocytes and spermatozoa, and the clinical practice of _in vitro_ fertilization and GIFT. We do both, recognizing that there is something of an anomaly in the fact that the therapeutic work is not research. Yet, in a sense it is. In this very early innovative state-of-the-art in which the success rate is deplorably low, each procedure is still very much an experiment. Clinicians are trying to improve their rate of recovering viable oocytes, their fertilization rate, the production of good embryos to transfer, the success rate of implantation, and so on. They are all working basically experimentally and we therefore regard this as a legitimate exercise of our oversight.

Furthermore, one major object of the regulation is to secure, if we can, public confidence in the procedure, a degree of mutual trust between the public and the practitioners, and to secure, so far as we can assure, that the practioners are acting worthily of that trust and that we can say so. There is therefore, justification for this dual, though confused, role.

The Voluntary Licensing Authority has published one annual report which included the Guidelines which we have issued for the direction of this work in the clinics and also recommendations which have a less compelling status than the Guidelines. We regard the acceptance of the Guidelines as a condition of our license. A centre which would not accept our Guidelines, including I may say, complete compliance with its own local Ethics Committee, would lose its license and we should say so publicly. We cannot compel them to stop their practice, but at least we can let it be known to the public that they are practicing without the license of a reputable body acceptable on both sides.

In our second annual report, which will be published early next month, there will be revised Guidelines because we too are working experimentally. We are improving, we hope, our technique as we go and that improvement is shown in a strengthening of some of the Guidelines.

We are also trying to strengthen the constitution of the Ethics Committees by requiring that chairmen should have no commercial interest in the private institution which is running the centre; by this means we are trying to assure the integrity of the practice.

Now, our Guidelines differ, I think, at some points first in principle and then, therefore, in practice from those considerations which Professor Eser has put before us. We would find it hard, I think, to accept quite so sharp a distinction between the therapeutic aim and what is called in his summary purely biological research. I have also said why I believe this to be so. The procedure is still in its infancy, not yet in its adolescence. It is in its nature an experimental procedure designed primarily to improve the success rate in clinical practice; but that aim requires learning much more about the actual process of human procreation and its constituent biological activities. In the practice of permitted, regulated experiment we do not forbid the generation of embryos specifically for research and, we think, for compelling reasons.

It would clearly be monstrous to go on subjecting a woman to more and more invasive tests, hormonal treatment and so on, more and more laparoscopies or screening, to find out why she continues to be infertile when the cause may lie in defective sperm in her husband. The testing of the capacity and motility of sperm requires their being tested on oocytes donated for the purpose; that test involves testing their capacity to fertilize. You cannot search for some forms of male infertility without testing sperm on oocytes taken from consenting, donating women.

Furthermore, to restrict research to what we call "spare" or "surplus" embryos left over from implantation, that too has difficulties. They are in very short supply, especially when cryopreservation takes some for later attempts at implantation, and those not implanted are often not implanted because, on microscopic examination, morphologically they do not look good enough to implant. It seems odd to start conducting research to investigate normal metabolism and development when you are starting with hypothetically defective material.

In terms of economy of use, if your concern is to spare a dehumanizing wastage of human life or assault upon what is itself essentially potential human life, I would submit to you that permitting research with embryos generated ad hoc will probably achieve that economical result more quickly than acting simply empirically, waiting to see what happens in clinical practice, and with any spare embryos left over. We do insist, however, that embryos used experimentally should not be replaced in the uterus for gestation.

On what philosophical grounds can we do this? Professor Eser indicated that the polarized debate on whether the human embryo enjoys personality, whether legal or moral, or not, will not get us very far. Recognizing that those who oppose this research are probably incontrovertibly opposed to it and that they will not yield to the sort of argument which I have used, I am driven back myself to perhaps an unphilosophically formed hypothesis, but one which I think gives us practical ground for proceeding. It stands on our recognition of the preciousness of human life. Human life is uniquely precious. That is not to attribute to it absolute value, for reasons which Professor Eser cogently indicated. The preciousness of the given is axiomatic to our work. Were this preciousness, this sacredness, not assumed and taken for granted, then there would be no purpose in regulating the research and there would be no purpose in the clinicians' and the researchers' accepting regulation. It is because we are agreed on the importance in an ontological sense of the material being handled that we have to devise the best form of control which we can on what I may call a principled pragmatism. I am not ashamed to use that word, though earlier of course, when I was a young moralist "pragmatism" was a word which I would never have allowed to sully my lips.

If you would consider how deeply we human beings are immersed in that vast system of biological waste which is part of the evolutionary order, relate the millions of sperm wasted from every man throughout his life and the hundreds of thousands of ova shed from every woman throughout her life, and see this like the tadpole spawn and the beachmast and the acorns and the thistledown, you will realize how vastly wasteful the natural process is, and we are deeply involved in it. In my view, this intervention, both scientific and clinical, imposes some measure of economy upon that vast wastage of human genetic material. The genetic material in the gametes and in the embryo may well express itself and - if everybody is very lucky - express itself in the form of a child. If it does not or if it is not even sent forward on that process but is used experimentally, this genetic information in the gametes and in the embryo can be read by those trained and competent to read it. The information read in the genetic coding can be formed into knowledge and that knowledge put to scientific use of vast potential benefit to human kind: partly in the relief of infertility; partly in all the contingent related studies, like genetics, oncology, immune response and so on; partly also, another necessity in this world, in the further search for reliable and acceptable contraception.

We believe that the importance of this scientific research is sufficient to rebut the presumption in favour of continuance of this precious life in the germ cells, permitting us to do it under careful regulation.

One or two contingent things attach to that. We, of course, set limits to the time when experiment is tolerated and, with other countries, this limit is at this moment about fourteen days. This position is morally and philosophically defensible in terms of the emergence of an individual organism sufficiently organized to be the grounds of a potential person. I think that sort of defence cannot be strongly and cogently made for any later stage like the beginning of sensitivity. That is the supposition on which at least we work.

As for the use of older fetal material in research, I believe the scientists who would want to work on that are a different order from the cellular scientists who are working with the pre-embryo. Their concern is with fetal tissues and so on. Research with that is well-established and involves less cultural problems. The people at the cellular level have no incentive to want to push this fourteen days boundary far beyond fourteen days, because another order of scientists takes over at that point of embryological study and they have material available to them through aborted material, whether spontaneous or induced.

One little matter has changed in our thinking. The Warnock Report did recommend storage up to ten years. In practice, this is now modified. The better centres, where there is real philosophical and principled thinking controlling their practice, arrange a contract with their patients for two years storage at a time. At the end of that two years, they are asked whether they have good reason to continue the storing of cryopreserved embryos. If they have, the contract will be renewed for another two years, as required. The notion of indefinite storage, even going as far as ten years unexamined, is now repudiated by those deeply concerned.

There is certainly a semantic error in the Warnock report in this matter. They speak about a right of disposal lying with the storage authority in the event of the parents' death. The word "right" is wrongly used. It should be a "duty" of disposal, because we cannot ethically leave the world cluttered up with this sort of material.

That is the initial response I would give to the excellent provocation to thinking which Professor Eser has given.

P.S. The substance of this comment is amplified in a work published after the Conference: The Status of the Human Embryo: Perspectives from Moral Tradition. Edited by G.R. Dunstan and Mary J. Seller, London: The King Edward's Hospital Fund, 1988.

Document 9

ETHICS REVIEW OF PILOT STUDIES AND THE INTRODUCTION OF NOVEL THERAPIES
EXAMEN ETHIQUE DES ETUDES PILOTES ET INTRODUCTION DE NOUVELLES THERAPIES

Henry Friesen

Discussion: Evangelos Garelis

Session G / Séance G

International Summit Conference on Bioethics
Colloque international de bioéthique

Ethics Review of Pilot Studies and the Introduction of Novel Therapies

PRESENTATION: Henry Friesen

The increasing demand and insistence that the introduction of new diagnostic tests, new therapeutic agents, and novel therapies (e.g. operations, appliances, etc.) be supported by well documented evidence including carefully conducted scientifically valid tests is an acknowledged fact of life. Yet clinical science and medicine in the final analysis does not consist exclusively of randomized controlled trials or fully documented laboratory studies. Arguably in the majority of clinical situations confronted, decisions that are made routinely are not based on rigorously controlled, adequately executed and appropriately analyzed double blind, randomized controlled studies. It must be recognized and acknowledged that much of what we do in medicine and the related health disciplines has a less secure and solid scientific foundation than we would care to admit. The treatment of an individual patient by a physician in a sense is an experiment. And if we are frank about our experience, we will acknowledge that at times we have been both astonished and at other times dismayed and devastated by the outcome. In other words, the outcome of an intervention in any given patient is less absolute than we had believed or we would wish the patient to believe. These "surprise outcomes" may on occasion be immediate (e.g. allergic reactions) or late in their manifestation, that is years after the intervention (e.g. Creutzfeldt-Jakob Disease in children treated with growth hormone derived from human pituitaries; or vaginal cancer in offspring of women receiving estrogen during pregnancy, but where the cancer appears only at age 18 to 25). The history of medicine is replete with examples where well intentioned interventions produced results which later were deplored and which led to human disease and suffering which in retrospect, at least in some cases, might have been avoided.

It is evident that modifications and adaptations of current medical and surgical practice occur regularly outside the scope of formal research protocols and that these results when judged to be of interest (either beneficial or harmful) are reported in the medical and scientific literature. There is need for such preliminary but provocative new data ranging from brief observations that point to fresh leads or challenge existing views. Sometimes a brief case report or a few critical experimental observations that can be summarized in single table, letter or figure may be highly instructive and stimulate further work in a field. Presumably this is why the letters section of **The Lancet** makes for such interesting reading.

A specific example to illustrate how blurred the distinction between research and practice may be is to consider the case report which appeared in the 1980's of a patient who presented with evidence of excess growth hormone secretion. The patient was found to have an enlarged pituitary, operated upon, but regrettably the abnormally elevated serum growth hormone levels did not return to normal - "the surprise outcome". The interested practitioner wondered why and began to look for alternative explanations. It turned out the patient had a tumor of the pancreas which the doctor reasoned was producing a hormone which caused excess secretion of growth hormone by the pituitary. The patient's pancreatic tumor was removed, and within hours the elevated serum growth hormone returned to the normal range. The pancreatic tumor removed, turned out to contain as the physician had postulated vast quantities of the putative - growth hormone releasing hormone which was identified for the first time in the extract of this patient's tumor. The isolation of growth hormone releasing hormone (GHRH) from any tissue source had eluded two Nobel laureate teams for decades. As a result, GHRH was synthesized and tested and found to be highly effective in stimulating growth hormone secretion in normal subjects. It is now being used as a diagnostic test in patients who are not growing, as well as being examined as a therapeutic agent to promote growth in children who are growth hormone deficient. The research effort spawned by this one patient has mushroomed into a substantial industrial enterprise. Clearly not every interaction between patient and physician produces such an unusual sequence of events with such sanguine scientific dividends.

If we accept that research is exploring the unknown, then this saga is a story of clinical research. If we note the definition of "pilot" as one who leads or guides, and a pilot study as one in which preliminary experiments or tests are conducted, we would accept the sequence of events related as a pilot study. Yet, I am quite certain that neither the physician nor the institution would have felt it to be appropriate to draw up a research protocol on the investigation and treatment of the patient with the pancreatic tumor.

Incidentally, a number of ethical considerations outside the scope of this discussion might be raised, one of which is - should the patient who contributed the tumor which led to the structural identification of GHRH derive any benefit from the subsequent efforts which have led to the commercialization of GHRH.

It is evident from my analysis and experience that research, even very important research of the kind I have cited, does not and in my opinion should not come under the purview of a research ethics board or institutional review board. Medical practice and medical practitioners operate under and in a framework in which standards, quality assurance and audits etc. are part of their modus operandi. Given the constraints and concerns about malpractice which are operative today, at least in the North American milieu, it is likely that the average medical practitioner will not be overly venturesome in engaging in practice and therapeutic approaches which are beyond the norm. And if they do, there are mechanisms in place to address and confront such individuals.

Before launching a full fledged randomized control trial, it may be necessary to engage in pilot studies. It is often not appreciated that performing a weak trial however, has serious long-term drawbacks. First, results of a weak trial may foreclose for a long period the possibility of good evaluation by a strong trial. Second, a weak trial may leave a well established yet ineffective therapy in place for years to come. The losses associated with applying ineffective or less effective therapies to large populations soon outweigh the costs of careful trials.

When considering pilot studies it is important to consider its purpose. It may be to examine the value of 1) innovative therapy; 2) to explore an idea; 3) to explore the logistics and feasibility of conducting a research study and 4) to train people in new techniques, operations, etc.

The outcome of a pilot study may provide some guidance for a) design, b) implementation, c) logistics, d) side effects and e) measurements required for a full scale randomized controlled study.

Several ethical issues need to be raised in reference to pilot studies: a) Are the reasons for conducting the pilot meritorious? b) Is the design, methodology and number of subjects appropriate? c) If the pilot study is successful, will a full randomized control study follow?

Rather than discuss a range of ethical issues in the abstract, I have chosen to present specific examples (pilot studies) that raise a number of issues that are germane to this conference and which I hope prove to be of interest and will stimulate some discussion.

The first relates to a topic with which I have great familiarity. It concerns the subject of prolactin secreting pituitary tumors. When I began my research in this area, the conventional medical wisdom maintained that human prolactin did not exist as a separate pituitary hormone, that human growth hormone which had prolactin-like activity had evolved to take its place - admittedly, not an unreasonable suggestion as human growth hormone does have some prolactin-like effect. Ultimately however, my laboratory was successful in purifying human prolactin, developing methods for measuring it, and soon thereafter in establishing that over half of all pituitary tumors are prolactin secreting tumors. This fact could be readily documented by a simple test on patients suspected of harboring pituitary tumors. Because of the anatomic location of the pituitary, when tumors enlarge beyond the bony confines of their normal site, they impinge upon the optic nerves and cause a progressive loss of vision and ultimately blindness. It became evident from our studies that, if prolactin levels in serum were grossly elevated, the patients often had a very large tumor. The presence of visual impairment and characteristic x-ray changes confirmed this. Standard practice at the time held that this situation called for emergency neurosurgical intervention to arrest loss of vision and prevent total blindness. It was considered a semi-urgent matter.

In the mid 1970s we organised a multicentre trial in Canada of bromocriptine therapy using a drug which we first showed as remarkably effective in lowering serum prolactin, both in normal subjects and in patients with pituitary tumors.

Approximately 80 patients were treated with bromocriptine and in the vast majority elevated prolactin levels were reduced to normal; infertility which in females was a major presenting complaint was corrected and within 6 months 80% of women who desired to achieve pregnancy did so, altogether a gratifying result.

A Canadian doctor reported clinical results on one patient who had a very large pituitary tumor with impaired vision. He advised the patient to have her prolactin secreting tumor removed surgically immediately or risk blindness. The patient refused surgical therapy outright. The doctor, somewhat frustrated by the response, indicated that he would give the patient a drug, bromocriptine, which lowered her grossly elevated prolactin levels, but likely would do nothing for the pituitary tumor. At a follow-up 3 and 6 months later, there was marked improvement in the patient's vision, in fact it was now normal. Although many suggested it was fortuitous, I felt it was possibly related to an effect of bromocriptine which not only inhibited prolactin secretion but also tumor growth. As a result I drew up a protocol to treat patients with bromocriptine in a Canadian cooperative study. Patients with large pituitary tumors and visual field impairment would be offered an initial period of treatment with bromocriptine, coordinated with carefully monitoring visual field changes, PRL levels and if there were any hint of deterioration or progression of visual impairment, standard therapy; namely, neurosurgical removal of the tumor on an emergency basis.

The proposal clearly was not without risk. In some patients the progression to blindness, without treatment, can be quite rapid, presumably due to hemorrhage or edema or swelling of the tumor. When the protocol was examined by ethics review boards, it was felt that the danger of this novel therapy compared to standard treatment was too risky and centres refused. I understood the concerns and reluctantly, even grudgingly, accepted the collective wisdom of my peers in 1978-79.

Meanwhile, several additional other anecdotal reports similar to those documented by the Canadian endocrinologist appeared, and finally with the advent of CT scanning one report appeared with documented objective evidence of pituitary tumor shrinkage within days of the onset of treatment with bromocriptine. The tumor melted like snow on a hot spring day. Now, bromocriptine is standard therapy for the treatment of all patients with large prolactin secreting pituitary tumors who have impaired or threatened vision. In the majority of cases vision can be restored upon bromocriptine therapy. As a matter of fact, the likelihood of preserving and restoring vision with bromocriptine either as definitive therapy or as initial treatment to maximally shrink the tumor, facilitates surgery when it is subsequently carried out.

The ethical issues raised are several:

a. A pilot study protocol halted because of ethics review board refusal, yet subsequent evidence indicates the protocol and proposed therapy were meritorious.
b. The consequence of the refusal to approve a protocol likely destined a number of people to blindness, that in retrospect was preventable.

What ethical consequences does an ethics review board face when it fails to sanction a pilot study that subsequent events demonstrate had merit and indeed had substantial, even life-saving benefit?

The second example of a pilot study which I wish to present as a case study is the effect of cyclosporine treatment on insulin dependent diabetes mellitus. The diagnosis of type 1 diabetes carries a sinister prognosis with an overall mortality of 60 percent four decades after the initial diagnosis is made. Uremia is the cause of death in over 30% of patients. It is expected that within this time, 16% will be blind, 21% will have a myocardial infarction, 12% will have gangrene or have undergone amputation, and 10% will have suffered a stroke. In recent reports it was estimated that the relative mortality in comparison to nondiabetics is greater than ten times at any age, and that as many as 1.4% of the patients with juvenile onset insulin-dependent diabetes mellitus (IDDM) may die within the first 5 years.

Although the loss of B-cell mass at the stage of clinical expression of the disease is substantial, the capacity for partial recovery is demonstrated by the clinical remission phase of diabetes, which is apparent to varying degrees in most patients. During this phase there is partial recovery of endogenous secretion of insulin, so that good control of metabolism is relatively easily achieved with modest doses of insulin. This phase lasts for a few weeks or months, but is followed inevitably by increasing insulin requirement and inability of metabolic control associated with declining residual insulin secretion. Since it is believed that the complications of diabetes would be prevented or ameliorated by good long-term control of metabolism, the benefit that might follow - enhancement of preservation of this remission phase is apparent.

Compelling arguments support the hypothesis that type 1 (insulin-dependent) diabetes mellitus (IDDM) is autoimmune in origin. Cyclosporine is a potent immunosuppressor that acts mainly on T cell mediated immunity, particularly the production of lymphokines such as interleukin-2; therefore it is a good candidate for immunotherapy of IDDM. Clinical experience in organ transplantation indicates that in moderate doses this compound can be used safely for long periods and gives better results than conventional immunosuppressive drugs. The demonstration that cyclosporine prevents IDDM in BB rats prompted investigators to try the drug in the early phase of human IDDM.

Stiller and his colleagues from London, Ontario (University of Western Ontario) reported a pilot study in which they treated 41 insulin dependent diabetic patients with cyclosporine. Of 30 patients treated within 6 weeks of diagnosis, 16 became insulin dependent. Of 11 patients who entered the study at 8 to 44 weeks after diagnosis, only 2 required no insulin.

In the pilot study undertaken, it seemed that cyclosporine-a, given within 6 weeks of the onset of Type 1 diabetes mellitus, was effective in altering (decreasing) the need for insulin; in a substantial percentage of patients it allowed them to become insulin independent. Moreover, upon stopping the cyclosporine therapy, the signs, symptoms and laboratory manifestations of diabetes recurred within 60 days.

The problem remains that no good study has been done in attempting to withdraw insulin, without other intervention, in Type 1 diabetes, and hence no double blind study has been done.

Hence, on the basis of the data presented, it may be concluded that the pilot study appears to have achieved its objective of demonstrating an effect, that is, of ameliorating the clinical features of Type 1 diabetes mellitus. In addition, the data presented, although not entirely convincing, suggest that the short term risk thus far from cyclosporine-a therapy is reversible upon stopping or decreasing the dose of cyclosporine-a being administered.

The data available thus far indicate a series of untoward potential and demonstrable risks associated with cyclosporine. In addition to the renal effects, a variety of major and minor risks associated with cyclosporine are known.

Based on the foregoing information, it would appear that the development of a well-controlled double-blind clinical trial of cyclosporine-a in Type 1 diabetes mellitus would be warranted.

The rationale initially advanced favouring a pilot study of cyclosporine-a in Type 1 diabetes mellitus was that short-term immunosuppression (e.g. 3 to 6 months), would produce euglycemia without insulin therapy. The hope was that this euglycemia might be of substantial duration, perhaps even permanent.

The first results have demonstrated that this view has had to be modified. From the limited results of the pilot study, it is concluded that approximately 40 to 50% of patients given cyclosporine-a may not require insulin therapy as long as they are treated with cyclosporine. This would be a maximum estimate because with time some patients may suffer islet damage despite cyclosporine. Therefore the question of potential risk due to drug toxicity in treatment of diabetes with cyclosporine requires assessment of the risk of long-term and perhaps life-long treatment with this drug.

Put succinctly, is cyclosporine an alternative and potentially superior therapy than conventional management with insulin for Type 1 diabetes mellitus?

The answer to this question must come in stages and will, of necessity, be incremental. The initial assessment of risk (drug toxicity) should be sought during a controlled trial of about 18 to 24 months duration.

The first report of such a control trial was reported by a French multicentre trial in July 1986 in **The Lancet**. In a double blind trial involving 122 patients aged 15-40 years, at 9 months treatment 24% of the cyclosporine group and 6% of the placebo group were in complete remission ($P<0.01$). The principal side effect of cyclosporine was a modest and reversible increase in plasma creatinine.

A number of significant ethical challenges are posed by the cyclosporine studies.

1. As insulin dependent diabetes mellitus often presents in children, what is the legitimacy of proxy consent by parents?

2. Since the window of opportunity for intervention using cyclosporine is short lived (less than 6 weeks after onset of disease) are parents, faced with the emotional stress of daily insulin injections vs the prospect of no insulin injections, in a suitable emotional state to give informed consent. One must appreciate the distress parents face in those first few weeks after the diagnosis of diabetes.

3. Diabetologists in good centres are not all in agreement about the merits of the cyclosporine trial. To what extent must this information be shared with the parents or the patients?

4. Cyclosporine protocols initially mandated a termination date at 1-2 years. In several patients who had not required insulin while on cyclosporine, within days and weeks of cyclosporine withdrawal, full blown diabetic ketoacidosis reappeared requiring multiple insulin injections daily thereafter. How do you explain to the patient that this is ethical? Or is it?

When more deliberate approaches are made to examine specific clinical questions or research issues, it is generally accepted that the double blind randomized controlled trial is the standard scientific strategy for determining the efficacy of therapy or intervention. There are at least six identifiable prerequisites that require attention when considering a clinical trial of this sort.

1. The trial needs to be done in order to address a significant issue. Would the clinical trial affect the treatment of a large number of patients? Is the present treatment inadequate? Does the intervention have merit?

2. The question to be answered is appropriate and unambiguous.

3. The trial architecture is valid, that is, the design and instruments are appropriate.

4. Inclusion/exclusion criteria strike a balance between efficacy and generalizability.

5. The trial protocol is feasible. e.g. The number of patients included in the trial is such that the trial is possible; that the results will have clinical merit; that the investigator clearly understands and is willing to adhere to protocol requirements.

6. The trial administration is effective. i.e. The timing of collecting clinical data, the monitoring of the progress of patient information (e.g. adverse events) and the process of forwarding the information to the data centre is specified. Analyses of data will be done at specified intervals and there are specific criteria laid down for terminating a trial. The length of the clinical trial is adequate to prove or disprove the efficacy of the intervention.

Several case studies have been presented to stimulate discussion. The first example is the most fundamental kind of pilot study; namely, the piloting of a patient towards the correct diagnosis and therapy and in the process spawning a major scientific advance. The second example was a correct intuitive response to a difficult clinical situation (i.e. patient refusal of standard therapy) resulting in a "surprise outcome". The latter was the basis for a "pilot study" protocol which was not sanctioned because it was judged too risky; yet subsequent experience proved that the risk in practice was minimal and that the failure to implement the protocol likely was harmful. Finally, the examination of the effects of cyclosporine in the treatment of Type 1 diabetics raises a number of substantive ethical considerations that continue to challenge us all.

My rationale for presenting these "real life" situations is to ensure that in the discussion of ethical principles we remain sensitive to the challenges faced by those who seek to apply these principles in practice.

DISCUSSION: Evangelos Garelis

Professor Friesen's illustrative presentation raises two main points.

First of all it reminds us that our present time one-sided adherence to the elaborate double-blind controlled study model may mislead us into underestimating the value of the traditional sound clinical observation and open preliminary studies with only a few subjects.

Indeed, much progress in scientific knowledge has emerged from such studies. To cite only one example out of many, all major discoveries in psychopharmacology derived from "accidental" clinical observations and not from sophisticated clinical or preclinical studies.

The second point refers directly to ethical issues pertinent to pilot studies. From Dr. Friesen's examples, one is led to the conclusion that because of the peculiarities of pilot studies, ethics committees tend to be inhibitory or even directly prohibiting rather than permissive and encouraging. Such an attitude may at times impede scientific progress and actually deprive patients of some therapeutic benefit.

Are we then to recommend that pilot studies be exempted from the established ethical review process?

In attempting to answer this question, we should try to attain a more balanced view on the value of pilot studies. We should remind ourselves of the thousands of pilot studies that led nowhere or were even harmful to the experimental subjects. In retrospect, such studies are clearly not justified ethically. Even the term "pilot" may be a misnomer in some cases, in the sense that preliminary studies do not necessarily lead to more advanced stages of research.

It seems then that the solution of the inherent problems in pilot studies is not to bypass the ethical review, but to use corrective mechanisms. Such procedures may include participation of the investigator in the discussion by the review committee, amendments to the protocol, appeal mechanisms and possibly other measures that may emerge from the discussion.

Remarks on THE CONDUCT OF CLINICAL TRIALS OF MEDICINAL PRODUCTS IN EEC AND GREECE: ETHICAL CONSIDERATIONS

by Evangelos Garelis, EEC

One of the primary aims of all EEC Directives on pharmaceuticals is the protection of public health. This protection naturally includes ethical standards in the conduct of clinical trials required to apply for a marketing authorization of a drug.

Specific ethical considerations include (Table I):

1. Marketing authorization may be granted exceptionally without comprehensive data on therapeutic efficacy and safety when it would be contrary to generally accepted principles of medical ethics to collect such information (1).

2. Community Guidelines on the conduct of clinical trials. An advanced draft has recently been prepared by the efficacy working party of the Committee on Proprietary Medicinal Products (CPMP).

   As explicitly stated in this document (2), the solutions chosen in the protocol to deal with the specific problems of a particular clinical trial must be both scientifically sound and ethically justified. The responsibility for these requirements lies on the sponsor of the trial as well as the investigators themselves.

   More specifically the following ethical provisions are included in the Guidelines:

   a. The ethical standard and professional integrity of the investigators should be beyond reproach.
   b. No trial should be started before an independent review board or a similar institution dealing with research ethics has accepted the protocol.
   c. The ethical evaluation should be made in accordance with the Helsinki and Tokyo Declarations and their eventual later adjustments.
   d. Voluntary, informed and preferably written consent of the patient or healthy volunteer must be obtained. Consent may be withdrawn at any time.

e. The physician responsible for the trial should inform the subject verbally, and if possible also in writing, about:
   - the aim of the trial and the way in which it will be conducted, and the possible risks and discomforts involved,
   - the fact that a non-registered drug and placebo may be included in the trial,
   - the condition that withdrawal from the study will not in any way affect the subsequent optimal treatment of the patient, nor the doctor/patient relationship.

3. Ethical problems were also extensively discussed recently with respect to the question of protection of original medicinal products against unauthorized copying.

The case for long periods of protection, up to 20 years in some proposals, was put forth with very strong arguments, on the grounds of encouraging innovation and original research.

On the other hand, equally strong reservations on long protection periods were raised, mainly on ethical issues involved. It was thus argued that extended protection of the original preparation would lead to unnecessary - and unethical for that matter - repetition of both preclinical and clinical studies, by anyone interested in producing drugs containing the same active material as the original proprietary medicinal product.

the final compromise reached by the Council of EEC Ministers in December 1986 was a protection period of 10 years for biotechnology and other high technology products and a 6-year period for conventional drugs (3).

4. Of relevance to the deliberations of this Conference are the discussions held in an EEC special workshop on "The constraints in international clinical trials" (4). The general conclusions of this workshop include the following recommendations on the ethical aspects of clinical trials:

a. There is a need for uniformity in standards of ethical review in EEC countries. All institutions in which clinical research is conducted should have access to an ethical review committee and the composition of these ethical committees should be harmonized (lay members, etc.).

b. With regard to liability for injury and insurance against this, there should be harmonization of the provisions within the EEC and an independent arbitration committee should be set up.

c. Exchange of information about clinical trials performed in different countries and exchange of information between drug regulatory agencies is desirable and practicable.

The problem of harmonization is a predominant issue within the European Community. In the field of medicinal products specific guidelines, including ethical considerations, exist in most member states. There is however a significant degree of diversity at present (Table II). The CPMP Guidelines (2) which will be adopted in the near future should be a major step towards harmonization.

In Greece, Guidelines on the conduct of clinical trials (5) were published in 1985 by the National Drug Organization (EOF) and were widely distributed to physicians in the country. They provide for written informed consent, which can be withdrawn at any time, insurance of the patient or healthy volunteer and an independent review process. There are special provisions for research on pregnant women, minors and persons with restricted mental capacity. Studies on prisoners are banned.

In the case of children or mentally incompetent subjects, in addition to consent by the parent or guardian, consent by the subjects themselves should be obtained "to the extent that they realize the meaning of the trial and the possible dangers thereof".

The role of the ethics committee is played by the Board of Directors of the institution where the trial is to take place, as well as the Board of Directors of EOF. Experience has shown that this arrangement is not the best way to deal with ethical issues inherent in clinical trials and will have to be revised. The conclusions of this Conference may provide an appropriate basis for such a revision.

References

1. Council Directive 75/318/EEC, 20.5.1975 (O.J.L147, 9.6.1975).
2. Recommended basis for the conduct of clinical trials of medicinal products in the European Community. EEC/CPMP working party on efficacy of drugs, March 6, 1987 (Draft).
3. Council Directive 87/21/EEC, 22.12.86 (O.J. L15/36, 17.1.1987).
4. M.G. Bogaert, (ed.) Workshop "Constraints in International Clinical Studies", Gent, 1985.
5. Clinical trials of drugs. Syntagographia, 2,1 (suppl.), 1985 (in Greek).

TABLE 1

ETHICAL ASPECTS IN EEC REGULATIONS

1. Clinical studies not required for marketing authorization when contrary to generally accepted principles of medical ethics (75/318/EEC).
2. Community Guidelines for the conduct of clinical studies (Draft).
3. Problem of duplication of studies because of protection of original products (87/21/EEC).

TABLE 2
NATIONAL REQUIREMENTS FOR THE REGULATION OF CLINICAL DRUG TRIALS IN THE EEC

	MEMBER STATES											
	BE	DE	DK	ESP	FR	GR	IRL	IT	LUX*	NL	POR**	UK
AUTHORITY REQUEST												
Application	(+)			+		+	+	+	(+)			+
Notification			+		(+)	+				+		
Special form compulsory			+	(+)		+						+
APPLICATION/NOTIFICATION IS NEEDED IF THE TRIAL INCLUDES:												
Patients			+	+	+	+	+	+		+		+
Healthy volunteers			+	+		+	+			+		
New drugs			+	+	+	+	+	+		+		+
Marketed drugs:												
-accepted indications			+									
-new indications			+	+		+	+			+		+
DOCUMENTATION TO BE ENCLOSED												
Investigation protocol	+		+	+		+	+	+	+	+		+
Chemical and pharmaceutical data	+		(+)	+		+	+	+	+	(+)		+
Toxicology data	+	+	+	+		+	+	+	+			+
Animal pharmacology data	+	+	+	+		+	+	+	+			+
Human data (later phases)	+		+	+		+	+	+	+	+		+
ETHICAL REQUIREMENTS												
Submission to Ethical Committee	+			+			+	+	+			
Informed consent (if possible)	+		+	+		+	+	+	+			
Patient information compulsory		+	+	+			+	+				
Patient information in writing			+	+		+						
REGULATORY MEASURES/ REQUIREMENTS												
Qualifications of investigators		+		+	+	+	+	+		(+)		
Approval before start of trial	+		(+)	+		+	+	+	+			(+)
Agency interference possible			+	+		+	+	+				+
Side-effects report			+	+		+	+	+				+
Trial report			+	+	(+)	+	+	+		+		
Patient insurance compulsory		+										
Agency evaluation period (weeks) approx.	3		8	8		8	4					5

*It is assumed that the regulations for Belgium also apply in Luxembourg
**To be completed

TABLE 3

ETHICAL REQUIREMENTS FOR CLINICAL DRUG TRIALS IN THE EEC

	MEMBER STATES											
ETHICAL REQUIREMENTS	BE	DE	DK	ESP	FR	GR	IRL	IT	LUX	NL	POR	UK
Submission to Ethical Committee	+			+		+	+	+	+			
Informed consent (if possible)	+		+	+		+	+	+	+			
Patient information compulsory	+		+	+			+	+				
Patient information in writing			+	+		+						

Document 10

ETHICS ISSUES IN INDUSTRIAL RESEARCH
LA RECHERCHE INDUSTRIELLE: QUESTIONS D'ETHIQUE

Eiji Suzuki

Discussion: Per Juul

Session G / Séance G

International Summit Conference on Bioethics
Colloque international de bioéthique

Ethics Issues in Industrial Research

PRESENTATION: Eiji Suzuki

I. Outline of speech:

Chairman, ladies and gentlemen,

It gives me great pleasure to have this opportunity to present my views here at the Summit Conference on Bioethics.

For the last ten years, I have been involved in the development of life science and biotechnology in Japan through my activities on various committees in Japanese industry and government.

Mitsubishi Chemical Industries Ltd., for whom I have the pleasure of working, established its Institute of Life Sciences in 1971 as a basic organization for researchers in integrated life sciences, which covers even the social aspects of the life sciences.

Today I would like to discuss two topics. One is, of course, related to the assigned topic of "Ethics Issues in Industrial Research". This question is important to the industrial sectors which are charged with the development and marketing of drugs and clinical or medical equipment. With rapid progress of science and technology, the seriousness of this question will grow deeper in the future. The fact that these problems are considered at this conference along with problems on the part of medical doctors has a truly important significance.

Though I have experience in these matters as an industrial executive, I myself have no background as a researcher or medical expert. Furthermore, I do not have the confidence to talk persuasively on them to the experts present here. Therefore, I have gathered the results of discussions from specialists in my company and from a few friends and arranged them in a paper for distribution to you. I will give a summary of these later, but please refer to the materials I have given you for details.

The other question I will discuss is a review from the standpoint of the life sciences on wide ranging industrial activities of man.

As to the ethical problems in relation to life, it is of course important to hold specialized discussions on these from the standpoint of dealing with life. At times, however, it is also important to return to the fundamental concept of bioethics and re-question it. Only with the fundamental concept can we measure reason and rationality in the realm of tacitly acknowledged common sense in society.

Modern science has achieved tremendous progress in the last two centuries. However, human sentiment in this era of progress has not changed significantly from that of the Middle Ages and even from primitive societies when it comes to wishes for power and wealth, likes and dislikes, fear of the unknown and so forth. Furthermore, in these centuries, especially from the industrial revolution onward, the progress of technology has leaned more and more toward materialistic civilization, while wasting energy resources as it progresses. In other words, as technology spreads at a rapid pace it becomes more and more estranged from life. It has become a fact that the value standard of industrial activity standing on only profit and economic effectiveness has spurred such a discrepancy. Now we have reached a point where people are starting to re-examine these values, and, I would like to address this issue.

II. Ethics Issues in Industrial Research

I have been participating in discussions on such problems as a member of a round-table committee on life and ethics which was formed in 1983 as an advisory committee to the Minister of Health and Welfare in Japan. The majority of the themes discussed by the committee concerned were issues such as artificial insemination, the standards for determining brain death and issues surrounding organ transplants. The committee also discussed extensive problems influencing social norms, medication of a person in a vegetative state, surrogate births and the inheritance rights of individuals born from sperm of the dead and so forth. These were later officially released in the form of minutes of the conference. The progress of medical technology has created a stir from social, ethical and legal standpoints in regards to the practical application of medicine.

In my opinion, the social and ethical views which mankind has nurtured throughout his long history are important in themselves and the rapid advances in medical technology is creating a gap from common sense. In applying advanced medical technology, there is a need for the specialist to hold human sentiment and social or traditional common sense, as well as to endeavor to let the people understand the advantages and the substance of new technology.

In answering the questions proposed by the organizer, the first thing I would like to emphasize is that the manufacturer who deals in drugs and medical products should act with a strong sense of ethics, even more so than industries in other fields. The Helsinki-Tokyo Declaration as revised in 1975 refers to ethical standards of physicians and this reasoning is also applicable to business concerns in the related industries as a matter of course.

However, some of the individual items written in the accords will not always be directly implemented as they are due to differences in racial and religious attitudes, as well as historical differences of social norms. In Japan, for example, the concept of "informed consent" is one such problem. There has been quite a bit of discussion in Japan on informing patients suffering from fatal diseases such as cancer or diseases for which no adequate treatment exists, and also on obtaining consent for use of experimental drugs in which consent is a prerequisite on human subjects, but, to date, the general response has been negative.

Concerning guidelines on clinical trials with human subject, called GCP (Good Clinical Practices), an advisory committee of the Japanese Ministry of Health and Welfare has recently drafted and announced a basic proposal. From now on the problem will be debated from all sides. Informed consent and a line up of various questions will be debated, including contracts between industry and medical institutions and areas related to the extent and division of responsibility among them, the double blind test related to human rights of tested subjects and so forth.

Frankly speaking, in dealing with stipulations based on objective standards on such questions, Japan lags somewhat behind other developed nations. To put it more strongly, the Japanese prefer to maintain a gray zone between reason and sentiment and like to keep such matters as vague as possible. When an unavoidable problem arises, a solution is sought case by case with mature wisdom, or expediently otherwise.

One reason for this is perhaps that the Japanese tend to be more homogeneous than other nations in terms of race and sentiment. And, in the environment of this large village or family attitude, tacit consent is easily shared. The second reason is that Japanese society is basically secular and lacks the concept of an absolute god such as Christianity and Islamic religions. Consequently, their life-style does not stand on a rigid rule, and thus the Japanese are not essentially familiar with the concept of a "contract".

Among the Japanese, on the one hand, there is the idea of integrating "technique" with discipline of the spirit and there is also a sort of a religious notion, which could be referred as "Do", that may be interpreted as "the way" or "teaching" which is to cultivate one's spirit along with advancement in technical skill. For example there is "the way of the tea" (sado) or tea ceremony, the way of the flowers (kado) or flower arrangement. Then, there are also judo and kendo, all of which involved their own "techniques" which have become unified with the spirit of "zen", a way of Buddhism. In this respect, there is also the concept of "the way of medicine" (ido) in reference to the medical profession. The physician is like a priest who practices medicine as an art or technique, and based on respect for this, a strong sense of trust has built up between the patient and the doctor. Of course, contemporary Japan is not without its share of iatrogenic suits which are on the increase, and, the existence of commercialized medical institutions is often highlighted by journalists, so cracks are appearing in this simplistic trust. However, as long as the doctor treats the patient in good faith, even when he happens to make mistakes in administering treatment, in fact a psychological repulsion to litigation remains on the part of the patient.

Such circumstances as above are rather peculiar to Japan. It is unlikely that we will ever see such thinking on an international level. At the same time in today's society where science and technology are increasingly forcing themselves into the bottom of the human heart, it may be wise to reserve a buffer zone of ambiguity or a certain "allowance". I believe there are limitations to the ability to reason out questions of this nature only by the way of Western Civilization, which has blossomed out of contractual relationships based on deductive reasoning and reductive analysis, or principle and rule. I would like to point out that one of the characteristics of the mechanism of life is redundancy.

Regarding my personal views on the questions presented by the organizers, while I ask you kindly to refer to the paper, I would like to propose that the following two very concrete problems be looked into as subjects for review on an international collaborative working basis.

The first refers to confirming effectiveness and safety in research and development of the peptide drug through application of biotechnology. With human-specific peptide, there are limitations on testing the effectiveness and safety of this medicine on animals. Also, with certain diseases such as Alzheimer dementia which is particular to human beings, animals cannot be used presently for efficacy tests. Therefore, we must establish a novel standard for testing these aspects.

The second topic deals with pre-clinical testing on animals and clinical trials on human subjects. The Helsinki Declaration specifies that a sufficient amount of testing should be performed on animals before proceeding to trials on human subjects. But, a recent idea on pre-clinical animal tests is to reduce use of animals to as few as possible. Thus, there is an inconsistency among existing accords and thoughts in relation to the required degree of testing on animals before proceeding to trial on human subjects. We need to establish a scientific basis for the adjustment of opinions in this regard.

III. The Contemporary Meaning of Life Science

Next, I would like briefly to talk about the second topic. There are many problems which remain to be solved from various standpoints in modern society including population, environment or ecology, resources, and also problems in economic, social and cultural and international aspects and so forth. We might say that there remains a huge pile of unsolved problems, and conflict of interests and confusion are worsening. On the earth today, there are refugees suffering from serious starvation or internal disturbances. On the other hand in the advanced industrialized nations, people have a tendency to seek higher quality of life than a mere satisfaction with materialistic sufficiency.

The result of a national poll conducted on the opinion on life by the Japanese government was that since 1979 the percentage of people placing importance on the "wealth of spirit" exceeded the number of those who emphasized "sufficiency of materials". Since that time this trend has been continuing. At the same time, that tendency accompanies a change of people's sense of values which is shifting away from emphasizing support for national prosperity and social relation in general to an individualism-oriented attitude which weighs more on individual life, personal happiness and desire.

Many of the problems facing society today can be said to be a natural consequence of the development of "forceful" industrial society initiated by the industrial revolution. The flow of modern technology as seen in the steam engine, the gasoline engine, electrical power and the harnessing of nuclear energy exists in a different dimension from that of previous industrial technology in which agricultural and animal farming coexisted with life. Two concepts, the logic of physics and the mystery of life, stand in opposition. And it is inevitable that the modern technology which has been constructed and expanded on the foundation of the former will eventually lose sight of the social harmony with nature and human life.

The development of modern biology as represented by molecular biology gives us an expectation of bridging this gap. As we learned that life phenomenon could be understood via the logic of physical science as that life is a form of expression of genetic information, now we have found the possibility of fusing the wisdom of life with artificial technology for sublation in a common language. Surely, this is the real significance of life sciences in contemporary society.

IV. Toward an Era of Restorations of the Earth

The life phenomena is, as its principle performance, equitable with human industrial activities in the sense that it procures or consumes resources and energy to produce materials useful for maintenance and proliferation of itself.

However, life differs from man-made systems in that in the case of life, extremely advanced information and automation systems operate at the molecular level based on gene information. To improve economic efficiency in man's artificial industrial technology which lies far behind in terms of the information system of life, it is essential to enlarge facilities through centralization and to have market structures for mass production and mass consumption. Also, the modern economy of pursuing profit and efficiency by the private sector or the public has accelerated the materialistic wealth of our society and has also rapidly aggravated today's social problems.

Of course, modern technology is not simply sitting back with its arms folded and watching. The manufacturing plant is now systemized and has reached a fair degree of automation through use of computer software and Super LSIs which can be mass produced economically. As a result of this, a modern automobile plant, for example, now can supply cars of various types on the same production line to satisfy diversified users' needs.

Progress in information network technology also enabled us to minimize the size of production plants and disperse its location. Such technological progress and gradual shifting of social consciousness bring out a slow change in the concept of values, for which the optimization of economy was responsible.

On the other hand, even among scientists and philosophers, reflective debates leaning towards analytical methods of modern science are becoming popular. Can "the whole" be recognized as a sum of the individual parts? The parts work together to achieve functional unity and sometimes, even while each part is fused together to form a member of parts in higher degree of dimension. Perhaps a new approach may be needed to comprehend "the whole". Such a question springs up even in Western science. It is "life" that always lurks behind these viewpoints. The essential nature of life is a spontaneous and positive harmony between the individual part in various levels and the whole body. This type of harmony is the significant element most sought after in the restoration of the economy and international relations today.

Today, the U.N. and various other organisations have expressed a spirit of international cooperation toward solving problems related to destruction of the earth's environment which grows more prevalent everyday on a world-wide scale. At a special U.N. Committee meeting on the environment held in Tokyo this February, a Tokyo Proclamation was adopted to "build the common future through cooperation". However, to answer questions of how to interconnect situations such as the increase of population, the misuse of resources and the destruction of the environment, wisdom and collaboration are needed on a worldwide scale.

The last ten years of the 20th Century and the 21st Century will be an age of restoring the earth and it is a time when new concept of values are created. From this viewpoint, Japan has experienced a peculiarly related period during its Edo era.

In Japan's Edo or Tokugawa Shogunate over 250 years the country closed off its borders and 30 million people to outside influences.

During this period, the country had to be totally self sufficient without relying on foreign resources, technology and markets and by protecting its own natural environment.

One of the scholars who provided the reasoning for this was an agriculturist, Kumasawa Banzan (1659-1691) through his "Theory on Land and Water". Kumasawa's theory of land, and water was based on proposals related to forest and rivers, arable land, as well as social and political planning, and was built on the foundations of Japan's characteristically East Asian Forest terrain and its natural, geographical and cultural features. In the 17th Century he was probably unequalled as an administrator who realized the significance of preservation of land and water or in the modern sense "ecological economics".

That is to say, along with expounding on flood control and other maintenance works, from an environmental and economic standpoint, he also pointed out that unemployment, the appearance of lordless samurai, etc., high taxes and other social burdens were connected with the destruction of nature and the waste of human skills. There is a need to recognize that imagination and new breakthroughs come about when different cultures and values collide. I think it would be valuable if such oriental philosophy is re-discovered and learned from in connection with mending the problems of our world.

V. Conclusion

The two topics I have discussed here today, in addition to definite proposals, can be summarized as follows.

1. The recognition of the gray border area between the world of science and human mentality. No matter how much progress science may make, I believe it is certainly wise to preserve a certain area of "allowance" that exists in this buffer zone as it is.

2. We need to create new concept of values to guide our industries and economy of tomorrow on the pre-requisite of learning from and respecting life. This is perhaps not an easy task, however, endeavors in this direction will surely lead to the creation of an abundant 21st Century for man in both mind and spirit.

DISCUSSION: Per Juul

Dr. Suzuki very clearly stated the role and position of the industry. We all acknowledge, of course, the importance of the industry in the development of drugs. On the other hand this development gives rise to many ethical problems. The economics, the monopoly and the political strength of the industry are factors which we must accept whether we like it or not. The relationship between regulatory authorities, doctors and the drug industry must build on confidence and trust, as you have stated in your paper. With regard to the evaluation of applications for marketing a new drug, there are mainly professional problems as the drug must fulfill the requirements concerning quality, efficacy and safety.

Major ethical problems arise during clinical trials as we have been discussing.

On page two of his paper, Dr. Suzuki states that new drugs must be tested on "living things". At first I was surprised by the term "living things". After yesterday's discussions on embryos I may accept the words. The basic background for animal screening which Dr. Suzuki touched upon, is the thalidomide catastrophe 25 years ago. Today we believe or think that drug-induced damages to the embryo during the first weeks of existence lead to a spontaneous abortion. But of course we really do not know. Hence toxicologists are also very interested in the possible investigations on preembryos and embryos.

If I may digress, I shall draw your attention to an ethical matter which is worth considering. We discussed yesterday whether you should "store" pre-embryos for two or ten years. When we die, and hopefully we shall all die, at best some of our organs may live on for some years in a recipient. However, today some of our cells may live on forever. We transplant human cancer cells into immunodeficient animals, so called "nude" mice and rats. When I work with these animals in my laboratory, I sometimes think, that they are carrying cells from a breast cancer from a woman who died several years ago. They are living cells of a patient who died several years ago -- and she provided her cells for research without any informed consent. The world of bioethics is a strange world.

I shall return to the subject in question. On page three, Dr. Suzuki mentions good clinical practice. I sometimes feel a little ashamed professionally that it has been necessary to prepare guidelines on good clinical practice and I would like to know what are the content and status of good clinical practice guidelines developed in Japan.

On page seven Dr. Suzuki states that "In short, the doctors ought to cooperate for the development of new drugs as long as they are confident of therapeutic advance and the possibility of the drug in question for contribution to the welfare of the patients and the society." I would if I may add a single word to this important thought, I would say that, "In short the doctor ought only to cooperate for the development. That would solve the vast majority of the ethical problems in my every day life.

With regard to ethical problems I shall present only a few points of importance concerning the information and justification of trials in humans.

First you mentioned problems with regards to biotechnology. We all recognize the problems involved with the evaluation of biotechnologically derived drugs or high-technology drugs. At present, the EEC, like many other organizations and individual countries are preparing guidelines concerning this difficult problem. There is no actual solution, for this is one of the fields where advances are made very rapidly.

With regard to animal experimentation, I can similarly say, that in the EEC as well as in the Nordic countries, a set of rules concerning the use of animals in preclinical experimentations are set and rather rapidly revised. Recently, we, for instance, changed our requirements with regard to the so-called LD50 which we considered an unethical and partly useless exercise which has killed millions of animals. Similarly, we are trying to reduce both the numbers of animals and the duration of the preclinical toxicity experiment.

I would like to see the following four points incorporated routinely into the clinical trials protocol:

1) information on the reasons for carrying out investigations in countries outside the country of origin.

2) information for authorities and participants in clinical trials about clinical trials carried out simultaneously. This concerns the actual phase three randomized clinical trial as well as pilot studies and phase one studies.

3) information concerning responsibility, liability and insurance.

4) information as to resources (including the economics) involved in the trial. The reason for this is that the scientific ethics committees are normally set up in the interest of the individual. However, in a time with limited resources their job might well be viewed in a broader

context. I do not care whether the research in question is funded by national organizations or not. To the final end, the patients and society pay every single cent. From the point of view of a national or international regulatory authority, I sometimes speculate, since we do not get this information, whether we are dealing with ethics of luxury. This point is perhaps a little controversial.

Document 11

ETHICS STANDARDS FOR RESEARCH ACROSS NATIONS AND CULTURES
NORMES D'ETHIQUE POUR LA RECHERCHE INTERNATIONALE ET INTERCULTURELLE

Z. Bankowski, J.F. Dunne, and S.S. Fluss

Discussion: Edmund Pellegrino

Session G / Séance G

International Summit Conference on Bioethics
Colloque international de bioéthique

Ethics Standards for Research across Nations and Cultures

PRESENTATION: Z. Bankowski*, J.F. Dunne, S.S. Fluss*****

PREFACE

The Council for International Organizations of Medical Sciences (CIOMS) is an independent, international, nongovernmental scientific organization which was established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO). Its primary function is to act as a sounding-board for drawing attention to and disseminating informed consent on new developments in biology and medicine, and to explore their social, ethical, moral, legal and administrative implications.

One of the most ambitious tasks of CIOMS to date has been the formulation, in collaboration with WHO, of Proposed International Guidelines for Biomedical Research involving Human Subjects (published in 1982). The ethical principles that should guide the conduct of biomedical research involving human subjects had been set forth some years earlier in the World Medical Association's Declaration of Helsinki, adopted by the 18th World Medical Assembly in Helsinki in June 1964, and amended by the 29th and 35th World Assemblies, held respectively in Tokyo in October 1975 and in Venice in October 1983. The reason that CIOMS embarked upon this project in 1978 was to demonstrate how these principles could be applied in practice, having regard to differing socioeconomic circumstances, varying national legal provisions and administrative arrangements, and to provide WHO with a set of standards for assuring the ethical acceptability of research studies which it sponsored.

CIOMS is uniquely suited for such a task. Its affiliated members include the national and international bodies representing many medical specialties. They constitute a particularly broad spectrum of medical opinion that CIOMS can consult and whose views can be reflected in its publications. Moreover, its status as a nongovernmental organization in official relations with WHO entitles CIOMS to report on its activities to the World Health Assembly.

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* Executive Secretary, Council for International Organizations of Medical Sciences, c/o WHO, Geneva.

** Chief, Pharmaceuticals unit, and Secretary, Secretariat for Research Involving Human Subjects, WHO, Geneva.

*** Chief, Health Legislation unit, WHO, Geneva.

The need for developing an operational approach to the ethics of medical research was immediately apparent from the support the project received. The stature and the experience of the special advisers and consultants to the project are self-evident, and they represent a wide variety of countries, cultures and political systems. The feasibility of the task was rapidly assured by the degree of cross-cultural consensus that emerged during three supporting conferences held in Portugal, Mexico and the Philippines. The general applicability of the guidelines has since been confirmed in the course of debate in many countries and, in some, they have stimulated and influenced the promulgation of professional codes of practice and statutory provisions.

Thus, early misgivings lest intercultural differences might compromise, or even frustrate, the elaboration of global ethical norms proved unfounded. The ethical principles of research involving human subjects are identical everywhere. They relate to respect for human dignity, and protection of the rights and welfare of human subjects; and they demand exemplary standards of professional responsibility from the clinical investigator. They therefore reflect the very essence of civilized behaviour, regardless of ethnic and cultural differences.

A decade ago, when the CIOMS guidelines were being prepared, very few countries had made arrangements for assuring the observance of these principles. It was generally believed that freely-elicited informed consent, and liberty to withhold or withdraw collaboration at any stage without fear of prejudice, offered the only basis for protecting the individual's freedom of choice and ensuring that biomedical research found acceptance with opinion at large. Remarkably little attention had been paid to the means of assuring the observance of these safeguards, or even to the validity and quality of the consent procedure. It is now generally accepted that, unless the potential subject has the intellectual capacity and insight to comprehend fully the risks involved, consent merely represents innate confidence in the technical judgement of the investigator. It is evident that the inherent limitations of the procedure, and its vulnerability to abuse, render it inadequate as an exclusive means of protecting the rights and welfare of research subjects, and that it fails most decisively when the population from which the subjects are drawn is least fit to protect its rights.

The CIOMS guidelines consequently attach fundamental importance to the need for ensuring that every research project is sanctioned by independent representative professional and lay opinion. The principle of peer review, particularly when it is applied to the ethics of research, will, on occasion, inevitably be accepted with reserve and misgiving by professionals who are concerned to protect their reputations. However, mutual and constructive criticism between peers within the research community has long been recognized as the most direct means of assuring integrity and accountability in medical experimentation. More recently, investigators have come to terms with the need for independent assessment of competing research proposals as the fairest basis for allocating research funds. How they are increasingly faced with the need, in order to protect themselves from risk of being accused of professional misjudgement or negligence before the courts, to have assurance that their activities are consonant with prevailing scientific and ethical norms. Ethical review committees are thus widely accepted as an essential element in the administration of medical research; wherever they have been introduced they have come to regarded as indispensable to the protection of subjects and investigators alike.

The creation of such committees is a prime example of the reactive or responsive nature of ethical norms. The main principle of ethics is generally acceptable but ethical norms have always reflected social values. They are not fixed or immutable; rather they are adapted - often impeccably - to the evolving needs and perceptions of the society they are intended to serve. Fundamental advances in medical technology are rarely devoid of ethical challenge. Unless society is prepared to address and, when necessary, to readjust to such challenge, important opportunities for therapeutic advance may well be lost.

CIOMS, in proposing the international guidelines, was seeking to reflect a durable consensus of matters or broad general principle. It did not seek to obtain consensus on issues on which, because of associated controversy or rapid technological advance, it would be premature to try to formulate internationally agreed recommendations. These very issues, however, are a prime focus of concern at national level, and CIOMS has a responsibility to ensure that they are subject to international discussion. However, if they are to be constructive, its interventions must wait until the competent and responsible national bodies are likely to be receptive.

Two such initiatives have been taken since the guidelines were published and others are now in prospect. One relates to the bioethics of human reproduction. The recent expansion of the needs for and the means of fertility regulation has raised a host of fundamental moral and ethical issues. In 1988 in Bangkok CIOMS will hold a conference, co-sponsored by WHO, on "Ethics and Human Values in Family Planning". Its objectives will be to stimulate an international, transcultural dialogue on rights and responsibilities of individuals and societies regarding their decisions on reproduction, and to encourage interaction on ethical issues among policy makers, health professionals, scientists, ethicists and the public.

CIOMS has been active also in promoting discussion of the ethical aspects of drug development. Unless society is prepared to accommodate to, and endorse, a position in which remote risks to the individual are accepted as a corollary of modern medical care and therapeutic progress, the whole basis of contemporary drug development will ultimately founder. However, this argument can be convincing only if assurance can be provided that a responsible and committed effort is in hand to minimize drug-induced injury, and if the risks of such injury can be shown to compare favourably to those accepted in other aspects of daily life. Over the past twenty years there has been reluctant acceptance on all sides that some aspects of drug's performance can be definitively established only from cumulative experience of its use in practice. Emphasis has shifted only very slowly, in drug safety assessment, from a primarily experimental strategy based upon rigorous toxicological screening in laboratory animals to a more balanced combination of toxicological evaluation and post-marketing surveillance.

Drug surveillance is undertaken through clinical observation of treated patients. To admit its necessity is also to admit, in principle, the need to utilize clinical records for research purposes. The debate continues on the extent to which this is ethically admissible and, if so, how personal privacy can be adequately protected. CIOMS has broached this concern and many other related issues in a recently published report on Monitoring and Assessment of Adverse Drug Effects. This report reflects the views of representative professionals directly concerned with the problem from various standpoints and these will need to be subjected to further discussions before any consideration can be given to the development of relevant international guidelines.

Meanwhile, the emergence of AIDS has raised an entirely new range of issues regarding confidentiality of information, and it has also lent urgency to the need to re-evaluate ethical norms concerning vaccine development, organ transplantation, and the use of plasma-derived biological products.

It was considered useful for the deliberations at this Conference to make available to the participants a concise overview of international instruments and codes, as well as the legislation, guidelines and codes of ethics relating to research involving human subjects in the seven countries represented at the Conference. This overview is intended to be descriptive rather than analytical.

HUMAN EXPERIMENTATION: A CONCISE OVERVIEW OF INTERNATIONAL INSTRUMENTS AND LEGISLATION, GUIDELINES, ETHICAL CODES, ETC. IN THE SEVEN SUMMIT COUNTRIES

Information document prepared for International Summit Conference on Bioethics, Ottawa, 6-10 April 1987

This paper has been prepared by the staff of the Health Legislation unit of the World Health Organization (WHO), in close cooperation with the Secretariat of the Council for International Organizations of Medical Sciences (CIOMS). It is intended to be descriptive rather than analytical; any views expressed are not necessarily those of WHO. The major contribution of Dr. J. Lau Hansen, a member of the staff of the WHO's Health Legislation unit, in the preparation of the overview is gratefully acknowledged.

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1. INTRODUCTION

1.1 The publication by CIOMS in 1982 of the Proposed International Guidelines for Biomedical Research Involving Human Subjects, the outcome of a joint project of WHO and CIOMS represented a culmination of a long series of activities undertaken by CIOMS, with WHO support and substantial WHO input. Throughout the process, it had been perceived that the Proposed Guidelines could not be developed and discussed in a vacuum, i.e. it was deemed essential that information be compiled and made available on the existing international instruments and on regional, national, and (in some instances) subnational legislation, codes of ethics, guidelines, and the like relating to experimentation on human subjects. The background to and genesis of the Proposed Guidelines have been described elsewhere (1) although it is perhaps important to point out that they were endorsed in September 1981 by the 56th Session of the CIOMS Executive Committee and in October 1981 by the 23rd Session of the WHO Advisory Committee for Medical Research, and were recommended for wide distribution as a consultative document to ministries of health, medical research councils, medical faculties, relevant nongovernmental organizations, and medical journals as well as other interested institutions, including research-based pharmaceutical companies. The impact of the Proposed Guidelines on the policies of certain countries is already perceptible.

In the course of the XVth CIOMS Round Table Conference on "Human Experimentation and Medical Ethics" (held in Manila on 13-16 September 1981), a paper was presented that endeavoured to examine the extent to which the various provisions of the Proposed Guidelines were reflected in the legislation and codes of ethics available and accessible at the time to the WHO staff responsible for the Organization's Health Legislation Programme. (2) While the paper was neither comprehensive nor exhaustive (nor, indeed, analytical in nature), due to inevitable constraints, it was considered to serve a useful purpose, if only by drawing the attention of medical researchers, legal experts, ethicists, and others to little-known legal developments and even less-known (at least as far as frequency of citation can be used as a criterion) contributions to the literature, particularly in such key languages as German.

It was considered that the participants at the present Ottawa Conference could well benefit from what might be described as an update, reflecting developments since 1981 at the international level and in the seven countries represented. This update makes no pretention to being exhaustive or comprehensive, nor could it be, given obvious space constraints. It is not analytical in character since an authoritative analytical review would inevitably (and quite rightly) have to examine not merely legal, para-legal, and exhortatory instruments, codes, and guidelines but also the vast literature that has proliferated almost exponentially in this field in recent years, particularly in the Federal Republic of Germany and the United States of America - a body of literature that cannot readily be retrieved by existing computerized data banks such as MEDLINE, if only because so much of the literature appears in invaluable but often difficult to access sources such as books, conference proceedings, Festchrifts, and legal journals not generally or at least not systematically scanned by medical literature indexers and abstractors.

1.2 The period between 1981 and 1986 was marked by a growing awareness of the need for greater consideration of cross-national and cross-cultural perspectives and issues in studies on the themes under consideration at this Conference. The literature on the subject has been greatly enriched by such major published contributions as Research Ethics (the Proceedings of an International Symposium on Scientific Research Ethics, held in Oslo on 23-25 August 1982) (3), reviewed by Curran in the columns of a WHO journal in 1986. (4) Curran's review draws attention to the particularly significant contributions made by Tranøy, Gerald Dworkin, Riis, McCarthy, Fletcher, and Hermerén. There are also valuable internationally oriented approaches in Capron's contribution on "Human experimentation" in the important new compendium BioLaw, in an important paper by Bassiouni et al., published in 1981, (6) as well as in a 1986 book on medical research involving children, published in the United Kingdom. (7) As in the past, publications in the Federal Republic of Germany on this subject continue to display the authors'/contributors' awareness of developments and issues in other countries. Problems in informed consent in both the experimental and other contexts are discussed in depth in a particularly well-documented book published in Switzerland in 1986. (8) Although evidently not yet published, Duclaux's 1985 575-page doctoral thesis on "L'Expérimentation du Nouveau Médicament sur l'Homme: Etude de Droit Comparé", (9) will be an indispensable reference tool for future researchers in this field. One possible shortcoming of at least some of the contributions listed above has been their relative lack of awareness of what appear to be difficulties in transposing policy formulations and expressions into the specific contexts of developing countries.

1.3 The literature at the national level has likewise grown apace. Particularly noteworthy have been the successive reports of the (United States) President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, whose Final Report (aptly entitled Summing Up) appeared in 1983. Those reports (some of which involved participation by other agencies) likely to be of particular interest to the participants at this Conference are Splicing Life (1983), Protecting Human Subjects (1981), Implementing Human Research Regulations (1983), Compensating for Research Injuries (1982), Whistleblowing in Biomedical Research (1982), and The Official IRB (Institutional Review Board) Guidebook.

Also important is the second edition of Levine's Ethics and Regulation of Clinical Research, published in 1986.(10) A reviewer in the Yale Law Journal, commenting on the first edition, stated "If only one book in this field were to be read ... I would suggest it be this one by Dr. Levine." A more practically oriented compendium was published in New York in 1985, and will also be of interest to participants at this Conference.(11)

2. HISTORICAL PERSPECTIVES

2.1 There seems to be somewhat of a consensus that the first reported controlled clinical trial is described in the Book of Daniel in the Old Testament. To quote Forgács, speaking at the IIIrd Symposium on Clinical Pharmacology held at Greifswald, German Democratic Republic, on 20-22 June 1978: (12) "Submit us to this test for ten days. Give us only vegetables to eat and water to drink; then compare our looks with those of the young men who have lived on the food assigned by the king, and be guided in your treatment of us by what you see. The guard listened to what they said and tested them for ten days. At the end of ten days they looked healthier and were better nourished than all the young men who had lived on the food assigned them by the king." (Forgács goes on to comment that "It is not an overstatement to say that much less well-conducted clinical trials are published in the years of the last quarter of the present century."). Vilardell cites the same event in a recent paper.(13) Interestingly, there is no reference to this case in Howard-Jones' magisterial review of historical aspects of human experimentation,(14) although he does (unlike the vast majority of writers in non-Germanic countries) mention the important Prussian Ministerial Directive of 1900. Although today merely an historical relic, the lucidity and cogency of this text are remarkable, and a translation is appended as Annex 1. The background to this important event in the history of the regulation of human experimentation is clarified in a paper published by von Bar in 1901.(15)

2.2 In the 1981 review of legislation and guidelines presented to the Manila Conference, reference was made to the Circular of the then Reich Minister of the Interior of 28 February 1931, and it was pointed out that the Guidelines on innovative therapy and scientific experimentation contained in the Circular had been described as "clearer, more concrete and more far-reaching than both the Nuremberg Code and the (Declaration of Helsinki Recommendations)".(16) We are indebted to Sass for the clear exposition and analysis of these Guidelines contained in his 1983 paper. (17) Sass in fact advances the hypothesis that the Guidelines merit further analysis and "might be instrumental in achieving a better understanding of some of the current moral concern in regard to the regulation ethics (sic) in new therapy and human experimentation, as it is impressively detailed in Robert J. Levine's Ethics and Regulation of Clinical Research (1981 edition). The issues and the concerns raised in a book such as Levine's would be different had the Richtlinien of 1931 rather than the Nuremberg Code influenced the further development of the theory and practice of moral responsibility in clinical research." Sass goes on to make the no less important point that the "factually non-existent impact of the Richtlinien on subsequent research practices in the German concentration camps also makes the relationship between existing administrative regulations and actual professional practice a prime moral issue."

2.3 One element still missing, at least in sources available to WHO, is the text known as the Khabarovsk Rules, evidently formulated by a Soviet military tribunal following a trial of Japanese physicians accused of conducting unethical medical experiments on prisoners of war during the Second World War. Capron has described at least some of these experiments,(18) but makes no allusion to the Rules as such. WHO is continuing its efforts to obtain a copy of what is evidently an important instrument.

2.4 It is indeed interesting that in the United Kingdom the traditional approach to the control of human experimentation has been non-statutory, with reliance on voluntary codes rather than on legislation. The contrast with animal experimentation could not be more striking - witness the Cruelty to Animals Act, 1876, of which the cover pages are appended as Annex 2. This Act has only recently been superseded by new legislation. Although information is not available as to the precise events that led to the enactment of the 1876 Act, it certainly does draw attention to the fact that the authorities in the United Kingdom were aware of unethical practices in experimentation on animals at the time, and that it was deemed appropriate to enact legislation to deal with the matter.

3. INTERNATIONAL DEVELOPMENTS

3.1 In addition to the Proposed Guidelines referred to in section 1.1, reference should be made in the first instance to the Declaration of Helsinki, of which a new version (which can, for purposes of convenience and in conformity with accepted, though unofficial, style, be termed "Helsinki III") was adopted by the 35th World Medical Assembly, held by the World Medical Association in Venice in October 1983. This version introduces only insubstantive amendments as compared with the previous October 1975 version ("Helsinki II"). In view of the fact that many authorities are continuing to refer to Helsinki II, the official text of Helsinki III is appended as Annex 3.

3.2 Within the framework of the Public Health Committee of the Partial Agreement of the Council of Europe, 11 States (Austria, Belgium, Denmark, France, the Federal Republic of Germany, Ireland, Italy, Luxembourg, the Netherlands, Switzerland, and the United Kingdom) established a Committee of Experts on Human Clinical Pharmacology, and assigned it the task of defining problems of clinical pharmacology with a view to harmonizing procedures in clinical trials. A report was submitted by the Committee in April 1983 (the delegation of the Netherlands expressed a general reservation as to the contents of the report) and covered, *inter alia*, the following points: 1. Control by public authorities; 2. Requirements to be met before the administration of new drugs to man; 3. Civil liability for injuries sustained by subjects of clinical trials; 4. The conduct of clinical trials and the role of the clinical pharmacologist; and 5. Exchange of information. The findings of the Committee in regard to ethical aspects are reproduced below:

> "4.4 *Ethical conditions*
>
> 4.4.1 Clinical trials in man also raise very delicate problems of ethics. The question at issue is whether clinical trials should not first be submitted for opinion to ethics boards, particularly when they have no direct therapeutic bearing...
>
> 4.4.2 Three different situations are reported in Europe:
>
> - In some countries there are ethics boards, but an investigator may conduct a clinical trial without notifying the ethics board. Notification is therefore not a legal requirement.

- In other countries there are no ethics boards, but these countries are intending to introduce them and require that they be consulted, solely in the case of healthy volunteers.

- In yet other countries consultation of the ethics board is a legal requirement for all trials and it thus has legal status.

4.4.3 The Committee agreed in conclusion that although all doctors undertake to abide by the rules of medical ethics, consideration ought to be given to setting up special boards to deal with these questions."

3.3 Guidelines adopted in June 1983 by the Nordic Council on Medicines concerning clinical trials on drugs contain detailed provisions concerning: (1) consent of and information to patients/participants; (2) provision of information to staff; (3) ethical evaluation of trials; (4) reports on adverse reactions; (5) follow-up; and (6) insurance. The relevant provisions are reproduced below:

"10. Consent and information

Patients/participants

The patient/participant's voluntary consent to participation in the trial must be obtained. It should be clearly stressed that this consent can be withdrawn at any time. If consent cannot be obtained, the reason should be indicated.

The doctor or dentist responsible for the clinical trial should in advance inform the patient/participant verbally and if possible also in writing, about:

- the aim of the trial and the way in which it will be conducted, possible risks and discomfort involved
- the fact that a non-registered drug and dummy tablets (placebo) may be included in the trial

A copy of the written information should be submitted with the notification.

Staff

All staff members involved in the clinical trial (pharmacy, laboratories, special departments consulted etc.) should be informed about the intended trial. The doctor or dentist conducting the trial is responsible for this being carried out.

A written statement on how information and instruction will be given to the staff involved, should be submitted with the notification.

11. Ethical evaluation

An ethical evaluation of all trials should be made in accordance with the Helsinki Declaration approved by the 18th World Medical Assembly in Helsinki, Finland, 1964, and revised by the 29th World Medical Assembly in Tokyo, Japan, 1975...

12. Reports on adverse reactions

The doctor or dentist responsible for the trial must immediately report any serious and/or frequent adverse reactions to the drug regulatory agency.

13. Follow-up

The doctor or dentist responsible for the trial must inform the drug regulatory agency in writing if any major change in a previously submitted trial protocol is contemplated.

If the trial does not begin, or is interrupted before its purpose is achieved, the reason shall be conveyed in writing to the drug regulatory agency.

When the trial is completed, the doctor or dentist responsible shall report the results, including recorded adverse reactions, in writing to the drug regulatory agency.

If the clinical trial is performed in cooperation with the manufacturer or his national agent, the manufacturer/agent is jointly responsible for the report.

14. Insurance

Patients/participants taking part in the clinical trial should be satisfactorily insured against any injury during the trial."

3.4 In its Recommendation 1046 (1986) on reproductive technologies in research, adopted on 29 September 1986, the Parliamentary Assembly of the Council of Europe, "considering the progress made in the field of embryology, the variety of ethical opinions and the conflict between values which arise in relation to the use of human embryos and fetuses and the need of European co-operation", recommended, inter alia, that the Committee of

Ministers call on the governments of the Member States of the Council of Europe:

"i. ...

ii. to limit the use of human embryos and fetuses and materials and tissues therefrom in an industrial context to purposes which are strictly therapeutic and for which no other means exist, according to the principles set out in the appendix, and to bring their legislation into line with these principles or to enact rules in accordance therewith which should _inter alia_ specify the conditions in which removal and use may be undertaken for a diagnostic or therapeutic purpose;

iii. to forbid any creation of human embryos by fertilisation _in vitro_ for the purposes of research during their life or after death;

iv. to forbid anything that could be considered as undesirable use or deviations of these techniques, including:

- the creation of identical human beings by cloning or any other method, whether for race selection purposes or not;
- the implantation of a human embryo in the uterus of another animal or the reverse;
- the fusion of human gametes with those of another animal (the hamster test for the study of male fertility could be regarded as an exception, under strict regulation);
- the creation of embryos from the sperm of different individuals;
- the fusion of embryos or any other operation which might produce chimeras;
- ectogenesis, or the production of an individual and autonomous human being outside the uterus of a female, that is, in a laboratory;
- the creation of children from people of the same sex;
- choice of sex by genetic manipulation for non-therapeutic purposes;
- the creation of identical twins;
- research on viable human embryos;
- experimentation on living human embryos, whether viable or not;
- the maintenance of embryos _in vitro_ beyond the fourteenth day after fertilisation (having deducted any time necessary for freezing);

v. to provide appropriate sanctions to ensure the application of the rules enacted pursuant to this recommendation;

vi. to create national registers of accredited medical centres authorised to carry out such techniques and to make use of them for scientific purposes;

vii. to facilitate and encourage the creation of national multidisciplinary committees or commissions on artificial human reproduction involving scientific activities concerning genetic material, human embryos and fetuses - to guide and counsel the medical and scientific authorities, to follow and control the application of such techniques and to authorise specific projects in the absence of concrete legislation or regulation;

B. continue to study the problems relating to the use of human embryonic and foetal tissue for scientific purposes and prepare, on the basis of the points mentioned in sub-paragraphs 14.A.ii to vii, a European convention or any other suitable legal instrument which would also be open to accession by non-member countries of the Council of Europe;

15. Instructs its competent committees to prepare a report on the use of human embryos and fetuses in scientific research, taking into account the necessary balance between the principles of freedom of research and of respect for human life and other aspects of human rights."

Rules governing the use of human embryos or fetuses and the removal of their tissues for diagnostic and therapeutic purposes are attached as an Appendix to the above Recommendation.

Reference should also be made to Recommendation 934 (1982) on genetic engineering adopted by the same body on 26 January 1982. Among other provisions, the Assembly stated that "gene therapy must not be used or experimented with except with the free and informed consent of the person(s) concerned, or in cases of experiments with embryos, fetuses or minors with the free and informed consent of the parent(s) or legal guardian(s)". The Assembly stated that "outline regulations should be drawn up to protect individuals against non-therapeutic applications of (genetic engineering) techniques".

3.5 On 10 March 1987, the Congregation for the Doctrine of the Faith of the Holy See issued an "Instruction on Respect for Human Life in its Origin and on the Dignity of Procreation". (19) This specifically addresses certain matters dealing with research on human embryos and fetuses in the following terms:

"4. How is one to evaluate morally research and experimentation** on human embryos and fetuses?

Medical research must refrain from operations on live embryos, unless there is moral certainty of not causing harm to the life or integrity of the unborn child and the mother, and on condition that the parents have given their free and informed consent to the procedure. It follows that all research, even when limited to the simple observation of the embryo, would become illicit were it to involve risk to the embryo's physical integrity or life by reason of the methods used or the effects induced.

As regards experimentation, and presupposing the general distinction between experimentation for purposes which are not directly therapeutic and experimentation which is clearly therapeutic for the subject himself, in the case in point one must also distinguish between experimentation carried out on embryos which are still alive and experimentation carried out on embryos which are dead. If the embryos are living, whether viable or not, they must be respected just like any other human person; experimentation on embryos which is not directly therapeutic is illicit. (29)

No objective, even though noble in itself, such as a foreseeable advantage to science, to other human beings or to society, can in any way justify experimentation on living human embryos or fetuses, whether viable or not, either inside or outside the mother's womb. The informed consent ordinarily required for clinical experimentation on adults cannot be granted by the parents, who may not freely dispose of the physical integrity or life of the unborn child. Moreover, experimentation on embryos and fetuses always involves risk, and indeed in most cases it involves the certain expectation of harm to their physical integrity or even their death.

To use human embryos or fetuses as the object or instrument of experimentation constitutes a crime against their dignity as human beings having a right to the same respect that is due to the child already born and to every human person.

The Charter of the Rights of the Family published by the Holy See affirms: "Respect for the dignity of the human being excludes all experimental manipulation or exploitation of the human embryo". (30) The practice of keeping alive human embryos *in vivo* or *in vitro* for experimental or commercial purposes is totally opposed to human dignity.

In the case of experimentation that is clearly therapeutic, namely when it is a matter of experimental forms of therapy used for the benefit of the embryo itself in a final attempt to save its life, and in the absence of other reliable forms of therapy, recourse to drugs or procedures not yet fully tested can be licit. (31).

The corpses of human embryos and fetuses, whether they have been deliberately aborted or not, must be respected just as the remains of other human beings. In particular, they cannot be subjected to mutilation or to autopsies if their death has not yet been verified and without the consent of the parents or of the mother. Furthermore, the moral requirements must be safeguarded that there be no complicity in deliberate abortion and that the risk of scandal be avoided. Also, in the case of dead fetuses, as for the corpses of adult persons, all commercial trafficking must be considered illicit and should be prohibited.

5. How is one to evaluate morally the use for research purposes of embryos obtained by fertilization 'in vitro'?

Human embryos obtained in vitro are human beings and subjects with rights: their dignity and right to life must be respected from the first moment of their existence. It is immoral to produce human embryos destined to be exploited as disposable "biological material".

In the usual practice of in vitro fertilization, not all of the embryos are transferred to the woman's body; some are destroyed. Just as the Church condemns induced abortion, so she also forbids acts against the life of these human beings. It is a duty to condemn the particular gravity of the voluntary destruction of human embryos obtained 'in vitro' for the sole purpose of research, either by means of artificial insemination of by means of 'twin fission'. By acting in this way the researcher usurps the place of God; and even though he may be unaware of this he sets himself up as the master of the destiny of others inasmuch as he arbitrarily chooses whom he will allow to live and whom he will send to death and kills defenseless human beings.

Methods of observation or experimentation which damage or impose grave and disproportionate risks upon embryos obtained in vitro are morally illicit for the same reasons. Every human being is to be respected for himself, and cannot be reduced in worth to a pure and simple instrument for the advantage of others. It is therefore not in conformity with the moral law deliberately to expose to death human embryos obtained 'in vitro'. In consequence of the fact that they have been produced in vitro, those embryos which are not transferred into the body of the mother and are called "spare" are exposed to an absurd fate, with no possibility of

> their being offered safe means of survival which can be licitly pursued.
>
> 6. What judgement should be made on other procedures of manipulating embryos connected with the 'techniques of human reproduction'?
>
> Techniques of fertilization *in vitro* can open the way to other forms of biological and genetic manipulation of human embryos, such as attempts or plans for fertilization between human and animal gametes and the gestation of human embryos in the uterus of animals, or the hypothesis or project of constructing artificial uteruses for the human embryo. *These procedures are contrary to the human dignity proper to the embryo, and at the same time they are contrary to the right of every person to be conceived and to be born within marriage and from marriage. (32) Also, attempts or hypotheses for obtaining a human being without any connection with sexuality through 'twin fission', cloning or parthenogenesis are to be considered contrary to the moral law, since they are in opposition to the dignity both of human procreation and of the conjugal union*.
>
> *The freezing of embryos*, even when carried out in order to preserve the life of an embryo - cryopreservation - *constitutes an offence against the respect due to human beings* by exposing them to grave risks of death or harm to their physical integrity and depriving them, at least temporarily, of maternal shelter and gestation, thus placing them in a situation in which further offences and manipulation are possible.
>
> *Certain attempts to influence chromosomic or genetic inheritance are not therapeutic but are aimed at producing human beings selected according to sex or other predetermined qualities. These manipulations are contrary to the personal dignity of the human being and his or her integrity and identity*. Therefore in no way can they be justified on the grounds of possible beneficial consequences for future humanity. (33) Every person must be respected for himself: in this consists the dignity and right of every human being from his or her beginning."

3.6 As far as research in the field of psychiatry is concerned, paragraphs 9-10 of the 1977 Declaration of Hawaii of the World Psychiatric Association read as follows:

> "9. In clinical research, as in therapy, every subject must be offered the best available treatment. His or her participation must be voluntary, after full information has

> been given of the aims, procedures, risks and inconveniences of the project, and there must always be a reasonable relationship between calculated risks or inconveniences and the benefit of the study.
>
> For children and other patients who cannot themselves give informed consent this should be obtained from someone close to them.
>
> 10. Every patient or research subject is free to withdraw for any reason at any time from any voluntary treatment and from any teaching or research programme in which he or she participates. This withdrawal, as well as any refusal to enter a programme, must never influence the psychiatrist's efforts to help the patient or subject.
>
> The psychiatrist should stop all therapeutic, teaching or research programmes that may evolve contrary to the principles of this Declaration."

One of the provisions of Recommendation No. R (83) 2 of 22 February 1983 of the Committee of Ministers of the Council of Europe to Member States concerning the legal protection of persons suffering from mental disorders placed as involuntary patients provides that "Clinical trials of products and therapies not having a psychiatric therapeutic purpose on persons suffering from mental disorder, subject to placement, should be forbidden. Clinical trials having a psychiatric therapeutic purpose are a matter for national legal provisions".

3.7 Reference should likewise be made to the Principes d'Ethique Médicale Européenne, adopted on 6 January 1987 by representatives of 11 European countries and an observer from a twelfth country. These Principes include a rubric devoted to human experimentation. They are not examined here in detail since the precise status of the document appears (at the time of writing) somewhat uncertain.

3.8 On 15-16 December 1986, WHO convened Informal Discussions on AIDS Vaccine Efficacy Trials in Human Populations. An extract from the Report of this meeting is appended as Annex 4. One of the recommendations of the meeting was that WHO should establish, as soon as possible, a "mechanism to ensure the open exchange of scientific, social, and ethical information necessary for advance planning and international collaboration in the clinical testing of candidate AIDS vaccines, with particular attention to Phase 3 trials". It appears that this is the first occasion that international attention has been paid to the emerging ethical and legal issues raised by AIDS research.

4. CANADA

4.1 As far as is known, there is no national legislation nor indeed legislation in the different Provinces and Territories dealing with ethical aspects of human experimentation. It would appear that at present the guidelines used are those contained in the 64-page 1978 report of the Medical Research Council entitled Ethics in Human Experimentation (MRC Report No. 6). In October 1986, the MRC issued a "Discussion Draft of Revised Guidelines", indicating that the 1978 document was being superseded "because of the need periodically to update all ethical statements and to guide the review of new research developments..."(*) The new Draft is subdivided into two Parts. Part A (Principles) comprises the following Chapters: I. Historical development - research ethics; II. The nature of human research; III. The evaluation of risk and benefit; IV. Special types of research; V. Principles of consent; and VI. Confidentiality. Part B (Practice) includes an initial rubric entitled "Implementing ethical responsibilities" and the following Chapters: I. Responsibilities; and II. Procedures. A "Selected Bibliography of Codes and Guidelines for Protection of Research Subjects" is appended. This Bibliography provides useful information on international codes and existing national guidelines in Australia, Canada, France, the United Kingdom, and the United States of America.

4.2 In December 1985, the Health Protection Branch of the Department of National Health and Welfare issued "Guidelines for the Conduct of Clinical Investigations". These Guidelines are evidently intended for use by drug manufacturers in connection with the implementation of the relevant provisions of the Food and Drugs Act and the Food and Drug Regulations. The Guidelines cover such aspects as: the responsibility of the investigator; procedures for the protection of subjects; mechanisms for obtaining informed consent; the tasks of Independent Review Committees; the monitoring of adverse events; discontinuance procedures; adherence to the research protocol; accuracy of records; evaluation of data relative to safety and efficacy of the drug under investigation; and availability of study records.

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* Subsequent to the Bioethics Summit Conference, the MRC approved and released Guidelines on Research Involving Human Subjects, 1987, which is available free of charge from the MRC, Ottawa, Ontario, Canada, K1A 0W9. The new guidelines closely resemble the discussion draft.

4.3 In April 1983, the Canadian Nurses Association issued a statement entitled "Ethical Guidelines for Nursing Research Involving Human Subjects". This contains the following substantive rubrics: I. The scientific merit of the research; II. Human subject consent, protection and confidentiality; and III. The setting where research is done. A short bibliography is appended.

4.4 It would appear that research involving human subjects in the humanities and social sciences is governed by a document entitled "Ethics: The Report of the Consultative Group on Ethics of the Canada Council". This includes sections dealing with: ethical principles; special applications of ethical principles (including research on captive populations, and research on children); research on cultures, countries, and ethnic groups different from one's own; and institutional review committees. This and the other documents listed above undoubtedly merit wide circulation and distribution, particularly because of the clear and succinct way in which issues, procedures, and institutional mechanisms are examined and discussed.

5. FRANCE

5.1 An Order of 10 August 1976 establishing the protocol for the clinical testing of pharmaceutical specialties provides that clinical trials are to be carried out as controlled trials, the way in which they are conducted varying in each case as being dependent upon ethical considerations. It does appear that there is somewhat of a legal vacuum insofar as research on healthy volunteers are concerned, and any intentional infringement of bodily integrity constitutes a punishable offence under the Penal Code. However, interventions may be permitted for immediate or direct curative or therapeutic purposes for the benefit of a single individual, although not necessarily for the benefit of others or for the sake of scientific knowledge. It would appear that even the free, informed consent of healthy volunteers does not constitute a defence for persons conducting non-therapeutic interventions in the event that any injury occurs (20).

5.2 Some general guidance for investigators is provided in a 1979 report of the Ordre National des Médecins entitled Déontologie des Essais Thérapeutiques, which emphasizes the need for strict scientific principles and fairness towards and respect for the patient. Sections 18 and 19 of the Code of Medical Ethics, adopted by Decree No. 79-605 of 28 June 1979, read as follows:

> "18. In investigations or interventions that he performs, as well as any therapeutic procedures that he prescribes, a physician must refrain from placing a patient at undue risk.
>
> 19. The use of a new therapeutic procedure on a patient may be envisaged only after adequate biological studies, conducted under strict surveillance, and solely if the therapeutic procedure in question can be directly beneficial to the person."

5.3 On 28 January 1983, the National Council of the Ordre National des Médecins issued a commentary on Section 19 and this is appended as Annex 5.

5.4 In a 1982 report entitled La Déontologie Médicale à l'Hôpital Public, the Ordre National des Médecins has stated that the following are not permissible in the context of therapeutic research:

- unnecessary trials;
- trials that are poorly conducted, poorly supervised, or the results of which are published too rapidly;
- the termination, for the purposes of a trial, of necessary treatment; and
- the use of patients as trial subjects for the testing of medicaments that are of no benefit to them.

5.5 Over the course of the last few years, a number of legal provisions have been enacted providing for the establishment of various administrative and consultative bodies with responsibilities in the fields of drug research and experimentation, and other aspects of medical experimentation. Perhaps the key development was the Decree of 23 February 1983 establishing a National Advisory Ethical Committee for the Life and Health Sciences, presided over by Professor Jean Bernard. The tasks of this Committee are to give its views on ethical problems raised by research in the fields of biology, medicine, and health, irrespective of whether these problems concern individuals, social groups, or society as a whole. In general, the Committee's statements are issued in the form of "Opinions (Avis)".

5.6 A particularly important development was the presentation in 1985 by the then Government of a Bill on studies in human subjects of medicaments or candidate medicaments (outside the framework of any care procedure) (Projet de Loi relatif aux essais chez l'homme d'un médicament ou d'une substance susceptible de le devenir, en dehors de tout acte de soin.) This Bill addresses many of the issues under discussion at the present Conference, comprising the following Divisions: I. Conditions governing trials; II. Advisory committees for trials of medicaments or candidate medicaments; III. Relations between research promoters and persons agreeing to participate in a trial; IV. Compulsory insurance; V. Provisions relating to social protection systems; VI. Administrative measures and penal provisions; and VII. Miscellaneous provisions. For reasons that are beyond the scope of this document, the Bill was eventually withdrawn by the Government.

5.7 On 15 December 1986, the National Advisory Ethical Committee for the Life and Health Sciences issued an "Opinion on _in vitro_ research on human embryos and their use for medical and scientific purposes". One of the main sections in this highly important Opinion is devoted to "Recommendations concerning _in vitro_ research on embryos". Substantial extracts from this Opinion will be published in a forthcoming issue of the _International Digest of Health Legislation_, but copies of the French text can be made available, on request, to participants at the Conference. The Opinion was accompanied by a lengthy "Ethical Report" and "Scientific Report", both issued on the same date (15 December 1986).

5.8 It is noteworthy that the quarterly journal published by the Committee (_Lettre d'Information du Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé_) contains information on developments in bioethics throughout the world. Indeed, the January 1987 issue contains an article by Judith Miller on the new Canadian Draft Revised Guidelines referred to in Section 4.1.

5.9 In an Opinion on patients in a chronic vegetative state, issued on 24 February 1986, the Committee referred to above expressed its total rejection of experimentation on patients in this condition, duly confirmed. It noted that their vulnerability calls for an increased degree of respect for their integrity; they should not be considered as "test material" for use in the advancement of science. In another Opinion on ethical problems raised by trials of new therapeutic procedures in man, issued on 9 October 1984 and extending not only to clinical trials of drugs but also to experimentation on all forms of surgical, radiological, or other interventions for diagnostic, prophylactic, or curative purposes, the Committee stressed the fact that there is no clearcut distinction between ethical review and scientific assessment, noting that an experiment without scientific value is _ipso facto_ unethical. The Opinion deals with the basic principles to be observed, such as: the necessity for trials; the conditions for trials (prerequisites, scientific value, and risk/benefit ratio); the selection of subjects (patients/healthy volunteers); free, informed consent; and review by an ethical committee. The second part of the Opinion contains proposals for the establishment and working procedures of ethical committees.

6. GERMANY, FEDERAL REPUBLIC OF

6.1 No information is available to indicate that there have been any changes to the relevant provisions of the Medicaments Law (as promulgated on 24 August 1976) or the Radiation Protection Ordinance of 13 October 1976, provisions that were analysed in the paper presented to the Manila Conference. (21)

6.2 In 1985, an Interministerial Commission on in vitro Fertilization, Genome Analysis, and Gene Transfer, established by the Federal Minister of Research and Technology and the Federal Minister of Justice (known as the Benda Commission), issued its report. It is noted that, in principle, the obtaining of human embryos are justified only if they enable the diagnosis, prevention, or elimination of a disease in the embryo involved or if they could contribute to the development of precise, fundamental medical knowledge. Some members of the Commission did however not exclude the possibility of the deliberate creation of embryos with a view to carrying out research during the initial stages of cellular development, to the extent that these experiments could be basic for research purposes. The Commission recommended to the Legislature that all non-justifiable experimentation on embryos be prevented, with appropriate safeguards and penalties being established. It was recommended that cloning and interspecific transplantation and gene transfer be prohibited, with penal provisions introduced to serve as a deterrent. Various restrictions are likewise suggested in regard to genome analysis.

In February 1987, the Commission on the Potentialities and Risks of Gene Technology of the Bundestag issued its report; this contains further detailed information on this particular subject. (22)

6.3 On 4 October 1985, the Federal Chamber of Physicians adopted Guidelines for Research on Early Embryos. (23) Under Section 3 (Limitations on research), research on human embryos is not authorized if: (1) it could be performed on animals; (2) it does not serve any immediate or medium-term prophylactic, diagnostic, or therapeutic purposes; or (3) it does not comply with rigorous scientific and procedural standards. The Guidelines go on to specify that the use of human embryos for research purposes requires the informed consent of the genetic parents. Other restrictions relate to the in vitro development of embryos (not beyond 14 days), cloning, the creation of chimeras, and interspecific hybridization being planned. Under Section 4, research protocols are required to be reviewed by local and regional ethical committees. as well as by a central ethical committee. The text of the Guidelines is appended as Annex 6.

A detailed Commentary on many of the Sections accompanies the Guidelines.

6.4 On 15 May 1985, the same body adopted Guidelines for the conduct of *in vitro* fertilization (IVF) and embryo transfer (ET) as methods for treating human sterility. (24) Most of the provisions of the Guidelines deal with matters outside the scope of this document. Section 4.3 (Handling of embryos that are not transferred) states that, "in accordance with the World Medical Association's Declarations of Helsinki and Tokyo (sic)" embryos should not be subjected to ethically unjustifiable experiments. Hence, scientifically justifiable research on embryos not used for transfer purposes may only be undertaken after it has been scrutinized by an ethical committee on the basis of stringent standards and conditions, laid down in special guidelines. It is evident that the guidelines referred to are those discussed in section 6.3 above.

7. ITALY

7.1 It would appear that the principal provisions regulating the ethical aspects of clinical trials in Italy are contained in Sections 42-45 of the 1978 Code of Medical Ethics, which read as follows:

> "42. Clinical trials of new pharmaceutical products and of new therapeutic techniques are indispensable; however, such trials may only be conducted after extremely comprehensive and thorough tests on animals.
>
> 43. Clinical trials on humans, which shall always be guided by a deep sense of his responsibilities on the part of the physician and by the fullest respect for human rights, shall invariably require the consent of the subject. Such consent shall be freely given and, if possible, expressed in writing, on the basis of a full understanding of the matter, after the physician has informed the subject of the nature, objectives, and attendant hazards of the trials.
>
> 44. Guarantees of an ethical nature, which may be referred to the Governing Council of the Association of Physicians, and scientific guarantees, verified as to appropriateness and specific competence, independent of the person carrying out the trial, shall apply to trials of a medical or surgical treatment. In cases of disease which, in the current state of

medical knowledge, are incurable, and in the terminal stages of such diseases, the trial of new therapies and new surgical techniques shall require reasonable prospects of efficacy taking account primarily of the spiritual and physical well-being of the patient. The trial may not entail increased suffering for the patient. The protocols of all trials on humans, with particular regard to the research procedures, methods used, and reactions of the subject, shall be made public, independently of the results of the research.

45. Trials on humans, whether or not for therapeutic purposes, shall not be remunerated in any way, since the stimulus to research may consist only in the wish to increase scientific knowledge and to contribute to the general good. The physician, or group of physicians, carrying out the trial shall be entirely independent economically from any body having a commercial interest in promoting a new treatment or a new technical device." (25)

7.2 It has also been reported that the Italian procedures governing clinical trials in human subjects must comply fully with the general principles of Helsinki I and II. (26)

7.3 A Circular of the Minister of Health published on 6 March 1985 in Corriere Medico states that, pending the adoption of specific legislation, the preservation of embryos for, inter alia, research purposes, is prohibited.

7.4 Reference should also be made to legislation at the subnational level. In Umbria, Section 4 of Regional Law No. 46 of 30 August 1982 provides that (1) trials must be performed with respect for the individual; (2) the trials must not prejudice any citizen's right to health or make any distinction between citizens with regard to that right; (3) the patient's free, informed consent must be obtained in advance; and (4) specific trials (tolerance, safety, efficacy, etc.) are subject to approval of the Regional Technical Health Council. In Veneto, Section 4 of the Regional Law No. 7 of 25 January 1979 on the care of children admitted to hospitals in the Region prescribes that clinical trials may be performed on hospitalized children only if the attending health personnel have obtained the consent of the child's parents or legal guardians.

8. JAPAN

8.1 According to published and unpublished information, investigators in Japan conducting clinical trials are required to give appropriate scientific and ethical consideration to the rights of the research subjects. (27) In particular, the provisions of Helsinki I and Helsinki II and of a report of the Science Council of Japan published in 1972 should be complied with, as well as the relevant provisions of the legislation on pharmaceuticals. Particulars as to the conduct of clinical trials, from the ethical, managerial, and administrative standpoints, are contained in Section 67 (Standards for conduct of clinical trials) of Ordinance No. 1 of 1 February 1961 of the Ministry of Health and Welfare, as amended on 23 October 1984, for the implementation of Section 80-2 (Conduct of clinical trials) of the Pharmaceutical Affairs Law (No. 145) of 10 August 1960, as amended. These provisions are not reproduced, either here or in an annex, since the only available English versions are copyrighted.

8.2 In December 1985, a group of experts submitted a report containing "Proposed Standards for the conduct of clinical trials of new drugs". (28) These Proposed Standards are contained in a 30-page English-language document (likewise copyrighted), and participants at this Conference would undoubtedly benefit by reading, in particular, Chapter 7 (Protection of human rights of subjects).

8.3 On 1 October 1979, the Japanese Diet promulgated a Law on the Compensation Fund for Injury Due to the Adverse Effects of Medicaments on the Market or Undergoing Experimentation. No information is available to WHO concerning the provisions, status, or implementation of this Law.

9. UNITED KINGDOM

9.1 The position in the United Kingdom is rather complicated in view of the significant number of bodies and organizations that have been active in the field, given the fact that there would appear to be no statutory provisions currently in force. Moreover, it is not always easy for the outside observer to monitor and indeed interpret the relationship between different codes and other instruments. The narrative that follows is based on the best available information, and the WHO Secretariat would certainly welcome its attention being drawn to any errors, omissions, or misinterpretations.

9.2 As the Medical Research Council (MRC) pointed out in a Press Notice in May 1986, that body published a detailed statement entitled "Responsibility in Investigations on Human Subjects" nearly 25 years ago. It was originally published in the MRC's Report for 1962-63. The MRC has pointed out that the statement remains in force; the guidance it provides has been incorporated into advice issued subsequently by the Royal College of

Physicians (RCP) (see infra). The Council's position on informed consent and other ethical issues has been formulated as follows:

> "In general, the patients participating in them should be told frankly that different procedures are being assessed and their co-operation invited. Occasionally, however, to do so is contra-indicated. For example, to awaken patients with a possibly fatal illness to the existence of doubts about effective treatment may not always be in their best interest.
>
> The progress of medical knowledge has depended, and will continue to depend, in no small measure upon the confidence which the public has in those who carry out investigations on human subjects, be these healthy or sick. Only in so far as it is known that such investigations are submitted to the highest ethical scrutiny and self-discipline will this confidence be maintained. Mistaken, or misunderstood, investigations could do incalculable harm to medical progress. It is our collective duty as a profession to see that this does not happen and so to continue to deserve the confidence that we now enjoy."

9.3 The RCP's Guidelines were last revised in November 1984. (29). They cover many, if not most, of the issues being addressed by this Conference, and Sir Raymond Hoffenberg, the President of the College, will no doubt be dealing with their implementation in his presentation to the Conference. The table of contents of the Guidelines is appended as Annex 7.

9.4 In the course of 1986, the RCP issued two reports, of critical importance to those concerned with research involving human subjects. (30, 31) The cover pages of these reports are appended as Annex 8.

9.5 The British Medical Association (BMA) addresses the issue of research in human subjects in its Handbook of Medical Ethics. Relevant extracts are appended as Annex 9.

9.6 In 1978, the British Paediatric Association (BPA) set up a Working Party on Ethics of Research in Children. The Working Party developed Guidelines to aid ethical committees considering research involving children, subsequently accepted by the BPA. (33) The preamble to the Guidelines reads as follows:

> "These guidelines presume that four premises are accepted.
>
> That research involving children is important for the benefit of all children and should be supported and encouraged, and conducted in an ethical manner.

> That research should never be done on children if the same investigation could be done on adults.
>
> That research which involves a child and is of no benefit to that child (non-therapeutic research), is not necessarily either unethical or illegal. (*)
>
> That the degree of benefit resulting from a research should be assessed in relation to the risk of disturbance, discomfort, or pain - the 'Risk/Benefit ratio'."

They contain rubrics devoted to the following aspects: the definition of "risk"; the definition of "benefit", within the context of (1) non-therapeutic research, and (2) therapeutic research; X-rays and isotopes; parental permission and cooperation, agreement by the child; new drugs; and new immunisation procedures. The Guidelines are copyrighted and hence cannot be reproduced here.

9.7 The Association of the British Pharmaceutical Industry (ABPI) has issued a number of important guidelines and codes. Specific reference should be made to the following: Code of Practice for the Clinical Assessment of Licensed Medicinal Products in General Practice (April 1983); Clinical Trials - Compensation for Medicine-induced Injury (August 1983); Guidelines on Data Needed to Support the Administration of New Chemical Entities to Non-patient Volunteers (date uncertain, but subsequent to September 1984); and ABPI Guidelines for Medical Experiments on Non-patient Volunteers - 1984 Update. Owing to space constraints it is not possible to deal with these items, in spite of their undoubted importance, in detail.

(*) A child in this context is taken to include the infant from the time of birth (but not the fetus). Thereafter, an individual remains a minor until 18. The Family Law Reform Act (1969) provides that a minor who has attained the age of 16 has capacity to consent to surgical, medical, or dental treatment (which 'includes any procedure undertaken for the purpose of diagnosis ... and applies to any procedure ... which in ancillary to any treatment as it applies to that treatment'). This statute does not deal with consent for other procedures, e.g. nontherapeutic research, and therefore the general law applies to all minors until 18. Such law does not recognise any 'age of consent', for capacity to consent depends on the child's intellectual capability and the complexity of the procedure; age is simply one factor to be taken into account.

9.8 As far as medical devices are concerned, the Medical Sterile Products Association issued, in 1986, Guidelines for the Design and conduct of Clinical Trials for Medical Devices. (34) These include provisions on patient confidentiality, insurance aspects, consent procedures, and the conduct of clinical trials overseas.

9.9 This review of the United Kingdom situation would be incomplete without reference to the important and ongoing developments concerning research on fetuses and embryos. As early as 1972, the Department of Health and Social Security (DHSS) in London and its Scottish and Welsh counterparts issued a report of an Advisory Group on the use of fetuses and fetal material for research purposes. (35) In 1982, a Committee of Inquiry into Human Fertilisation and Embryology was appointed by the four Health Ministers in the United Kingdom, the Secretary of State for Education and Science, and the Lord Chancellor. Its report (the Warnock Committee Report) received considerable attention in medical, legal, and scientific circles, as well as in the media (not excluding the popular press). (36) The MRC's response to this inquiry was published in 1985.

In January 1985, the MRC issued a revised statement (superseding a 1982 statement) entitled "Research related to human fertilisation and embryology", while the Royal College of Obstetricians and Gynaecologists (RCOG) issued a "Report of the RCOG Ethics Committee on In Vitro Fertilisation and Embryo Replacement or Transfer". Subsequently, a body known as the Voluntary Licensing Authority, with nominees from the MRC and the RCOG, as well a joint MRC/RCOG nominees, was established. That Authority has now issued Guidelines and these are appended as Annex 10.

9.10 Following these developments, in 1986 the DHSS issued a Consultation Paper discussing legislation on, inter alia, embryo research. (37) Some of the provisions of this paper relate specifically to research and are appended as Annex 11. The debate on this subject continues unabated, and participants in this Conference are referred, in particular, to the proceedings of a CIBA Foundation meeting on the subject. (38)

9.11 There has been some discussion in the United Kingdom on the appropriateness or otherwise of establishing a national ethical research committee. This and related issues are discussed in a recent paper by Short. (39)

9.12 Finally, reference should be made to the statement issued by the MRC in 1985 on "Responsibility in the use of personal medical information for research: principles and guide to practice". Its cover pages are appended as Annex 12.

10. UNITED STATES OF AMERICA

10.1 The outside observer witnessing the United States scene in the fields covered by this document cannot but be astonished - and deeply impressed - by the professional energy in Government, in the academy, and in "think-tanks" and elsewhere now being devoted to bioethics in general and to ethical issues in human experimentation in particular,and by the intellectual quality and sophistication of much of the output. One is constantly impressed by the studies and papers produced by a large number of individual investigators, physicians, lawyers, ethicists, philosophers, and others, as well as by various institutions. It would perhaps be invidious to mention individuals, but particular reference should be made to the materials and ideas emanating from the Hastings Center, now at Briarcliff Manor in New York State, and the Center for Bioethics at the Kennedy Institute of Georgetown University in Washington, D.C. The recent establishment of an International Bioethics Program at the Hastings Center is a welcome development. As regards documentation and publications, reference should be made to the regular volumes in the Bibliography of Bioethics and the now slightly dated but still essential Encyclopedia of Bioethics. These are indispensable tool for those in the field, as is what may well be the only journal specifically dealing with the work of ethical review committees, namely IRB. Reference has already been made to the important reports produced under the auspices of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

10.2 Another important and in some respects unique feature of the US scene is what one might describe as its glasnost (to use a word currently in vogue in another context). Thus, it is perhaps only in the USA that draft regulations, policy formulations, etc. are published for public comment in a journal, the Federal Register, widely accessible in that country, although certainly less accessible elsewhere and probably virtually unobtainable in many developing countries. One example is the "Proposed Model Federal Policy for the Protection of Human Subjects", issued in the form of a Notice of the Office of Science and Technology Policy of the Executive Office of the President and published in the Federal Register on 3 June 1986. Public comment, as well as comment on the part of the Federal agencies concerned, is specifically solicited, and it is indicated that the final Model Policy (taking these comments into account) will be published in due course in the Federal Register.

Another invaluable source of information is the published reports of hearings before committees of the United States Congress, publications that, unfortunately, are often not readily accessible outside the USA. We shall cite one example. On 1 July

1986, Professor Robert J. Levine (a Professor of Medicine at Yale University School of Medicine, and Chairman of its Institutional Review Board) provided testimony on issues in AIDS research to the Intergovernmental Relations and Human Resources Subcommittee of the Committee on Government Operations of the U.S. House of Representatives. (40) In his testimony, Levine concentrated on what he described as "two highly controversial aspects of development of new drugs for the treatment of AIDS". These were: (1) Is the placebo-controlled randomized clinical trial appropriate for the evaluation of these new drugs?; and (2) During the period of evaluation of new drugs should they be made available to patients with AIDS on a "compassionate use" basis?

We shall no doubt in the future be witnessing testimony before Congressional committees on some of the no less critical issues raised by the testing of candidate AIDS vaccines. Some of these questions were posed in the following terms by Lawrence K. Altman, medical correspondent of the New York Times; in an article published in the International Herald Tribune on 19 March 1987:

- How can studies prove that the experimental vaccine truly repels the invading AIDS virus, since all subjects must be warned to avoid exposure to a fatal disease?

- With whom would a study group of vaccine recipients be compared to see if they had been protected?

- Even if some subjects are exposed to possible infection, how long will it take to know whether protection has been offered against a disease that often does not develop for five or more years?

- Should the pressing need for a vaccine bring about decisions on testing and evaluation with much less data than it would have under ordinary circumstances?

10.3 Within the scope of this short document it is not possible to do justice to the US statutory or regulatory scene insofar as research in human subjects is concerned. (41) We shall mention here only some of the key developments in recent years.

10.4 The basic regulations for the protection of human subjects are contained in Part 46 (Protection of Human Subjects) of Title 45 (Public Welfare) of the United States Code of Federal Regulations, last revised on 8 March 1983. These now comprise the following Subparts: A. Basic HHS Policy for Protection of Human Research Subjects; B. Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization; C. Additional

Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects; and D. Additional Protections for Children Involved as Subjects in Research.

10.5 On 29 July 1983, new provisions inserted into Part 219 (Protection of Human Subjects in Department of Defense-Supported Research) of Title 32 (National Defense) prescribe that the use of prisoners of war as human subjects of research is prohibited.

10.6 It is understood that the Department of Health and Human Services (HHS) is now considering action on proposed regulations addressing research involving those institutionalized as mentally disabled.

10.7 The Food and Drug Administration (FDA), as well as other agencies, have their own regulations on research involving human subjects (in the case of the FDA, they are contained in Part 50 (Protection of Human Subjects) of Title 21 (Food and Drugs). One of the objectives of the Proposed Model Federal Policy referred to above is clearly to develop a coordinated approach to the subject. The Policy was based on the work of an Ad Hoc Committee for the Protection of Human Research Subjects, followed by subsequent deliberations by an Interagency Human Subjects Coordinating Committee. It may be mentioned in this respect that the agencies evidently involved in the development of the Policy included the Agency for International Development, the Department of Agriculture, the Environmental Protection Agency, the National Science Foundation, and the Central Intelligence Agency (the latter Agency is required by Executive Order 12333 to conform to the guidelines issued by HHS).

10.8 The FDA's new regulations for the submission and review of Investigational New Drug applications were published in the Federal Register on 19 March 1987. The text was not available to WHO at the time of preparation of this paper.

10.9 As far as statutes are concerned, Section 511 of Public Law 98-139 (an appropriations act for, inter alia, HHS) prescribes that none of the funds appropriated "shall be used to pay for any research program or project or any program, project, or course which is of an experimental nature, or any other activity involving human participants, which is determined by the Secretary or a court of competent jurisdiction to present a danger to the physical, mental, or emotional well-being of a participant or subject of such program, project, or course, or a participant's parents or legal guardian, if such participant or legal guardian, if such participant or subject is under eighteen years of age" (the Secretary of Health and Human Services is to adopt appropriate regulations respecting this Section).

The Health Research Extension Act of 1985 (Public Law 99-158) provides for the insertion in the Public Health Service Act of a new Section 498 (Fetal Research), reading as follows:

"FETAL RESEARCH"

"Sec. 498. (a) The Secretary may not conduct or support any research or experimentation, in the United States or in any other country, on a nonviable living human fetus ex utero or a living human fetus ex utero for whom viability has not been ascertained unless the research or experimentation -

"(1) may enhance the well-being or meet the health needs of the fetus or enhance the probability of its survival to viability; or

"(2) will pose no added risk of suffering, injury, or death to the fetus and the purpose of the research or experimentation is the development of important biomedical knowledge which cannot be obtained by other means.

(b) In administering the regulations for the protection of human research subjects which -

"(1) apply to research conducted or supported by the Secretary;

"(2) involve living human fetuses in utero; and

"(3) are published in section 46.208 of part 46 of title 45 of the Code of Federal Regulations;

or any successor to such regulations, the Secretary shall require that the risk standard (published in section 46.102(g) of such part 46 or any successor to such regulations) be the same for fetuses which are intended to be aborted and fetuses which are intended to be carried to term.

"(cX1) the Biomedical Ethics Advisory Committee appointed under section 381 shall conduct a study of the nature, advisability, and biomedical and ethical implications of exercising any waiver of the risk standard published in section 46.102(g) of such part 46 (or any successor to such regulations). The Committee shall complete the study and report its findings to the Biomedical Ethics Board established under section 381 not later than the expiration of thirty months after the date of enactment of this section. The report shall include the recommendations, if any, of the

> Committee on the advisability of the authority for such a waiver and the circumstances under which such a waiver might be granted. The Biomedical Ethics Board shall transmit the report to the Secretary, the Committee on Energy and Commerce of the House of Representatives, and the Committee on Labor and Human Resources of the Senate.
>
> > "(2) During the thirty-six month period beginning on the date of enactment of this section, the Secretary may not grant (under section 46.211 of part 45 of title 46 of the Code of Federal Regulations or any successor to such section) a modification or waiver for fetal research.
> >
> > "(3) Effective October 31, 1988, paragraph (2) is repealed."

10.10 There are also State statutes relating to research on fetuses, and according to a report in a recent US news magazine, approximately 28 States have adopted legislation either prohibiting or restricting such research. For example, Chapter 327 of the Laws of 1983 of Arizona provides that "no person shall knowingly use any component of a fetus or embryo resulting from an induced abortion for medical or scientific experimentation or investigation except to diagnose a disease or condition in the mother of (the) fetus or embryo" (the quotation is from the long title of the Act). According to Robertson, fetal research laws in at least six States could "now be read to prohibit embryo research of any sort". (42) Within the scope of this paper, it is not possible to deal with other State legislation regulating human research; the matter is briefly discussed in Capron's contribution to BioLaw.

10.11 The regularly updated Guidelines for Research Involving Recombinant DNA Molecules (the current version was published in the Federal Register on 7 May 1986) provide for special safeguards in the case of recombinant DNA research involving human subjects. Certain categories of such experiments require specific review by the Recombinant DNA Advisory Committee (RAC), a public advisory committee that advises the Secretary of Health and Human Services, the Assistant Secretary for Health, and the Director of the National Institutes of Health (NIH), concerning recombinant DNA research (such review is obviously in addition to standard Institutional Review Board review). On 29 September 1986, the RAC adopted "points to consider in the design and submission of human somatic-cell gene therapy protocols".(43) These apply only to research conducted at or sponsored by an institution receiving any support for rDNA research from the NIH.

10.12 This document would be incomplete if it failed to mention the recently issued "Guidance for Institutional Review Boards for AIDS studies", made available by the Office for Protection from Research Risks of the NIH. Major extracts from this document are appended as Annex 13.

10.13 At the State level, the only known statute that deals with AIDS research in a substantive manner is the Acquired Immune Deficiency Syndrome Research Confidentiality Act of California, approved by the Governor on 2 October 1985. Some of the relevant provisions are reproduced below:

> "**199.36** Prior to participation of an individual in a research study relating to AIDS, both of the following requirements shall be met:
>
> > (a) The informed consent of each research subject shall be obtained in the method and manner required by Section 46.116 (a) and (b), of Part 46 of Title 45 of the Code of Federal Regulations (see IDHL, 1976, 27, 222) and be documented in accordance with Section 46.117 of that part
> >
> > (b) Each research subject shall be provided with an explanation in writing, in language understandable to the research subject, of the rights and responsibilities of researchers and research subjects under this chapter.
>
> **199.38** In the event that the participation of an individual in a research study is disclosed, the information shall not be used to determine the employability or insurability of the research subject.
>
> **199.39** Nothing in this chapter shall preclude disclosure of information in order to further research efforts, including, but not limited to, the publication, dissemination, or sharing of raw data, statistics, or case studies, so long as no confidential research records concerning any research subject are disclosed".

11. CONCLUDING OBSERVATIONS

As the reader will have perceived, and as was clearly indicated in the Introduction, this document has been descriptive rather than analytical, since an analytical document would have involved almost insuperable structural difficulties, given the overlap of many of the statutory texts and other instruments discussed. The document has not addressed the crucial issue of the relevance of legislative and non-legislative developments in developing country contexts, in spite of the fact that the global community will become confronted with what appears to be the relative paucity of appropriate ethical review structures in many parts of the Third World. WHO is continuing to monitor and report on both legislative and non-legislative approaches to the problem. All relevant texts in these countries (as well as in developed market-economy and socialist countries) are being published in the International Digest of Health Legislation. It is hoped that this Conference will serve as a focus for developed and developing countries alike on the alternative approaches to resolve legal and ethical dilemmas in a manner that is consonant with human rights and appropriate to national contexts.

It should not be forgotten that Article 7 of the International Covenant on Civil and Political Rights, which entered into force on 23 March 1976, prescribes, inter alia, that "no one shall be subjected without his free consent to medical or scientific experimentation". We need to know how this provision should be implemented in countries where there is a host of pressing priorities in the health sector.

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DISCUSSION: Edmund Pellegrino

I would like to congratulate Dr. Bankowski for his efforts in bringing about the agreement on the principles respecting research involving human beings expressed in the CIOMS guidelines. This is a propitious beginning which should do much to assure the safety of research subjects, the continuance of the social sanction for experimentation involving humans and the moral validity of the enterprise of clinical investigation.

In the brief time I have I would like to move the discussion from the policy level to the microcosm of the clinical investigator. I wish to focus on what might be done to raise the ethical sensitivities of those who actually carry out clinical investigations. This is essential to the transcultural dialogue and the acceptance of the CIOMS and other global ethical directives.

The final common pathway for any international set of ethical guidelines is the physician-investigator, i.e., the clinical scientist. If there is to be global consensus on ethical guidelines, these guidelines must be intelligible and convincing to this group of medical scientists. It is they who design, monitor, initiate, and interpret, clinical studies. It is they whom the subject and society must ultimately trust to carry out the responsibilities of human experimentation in a morally sensitive way.

Agreement among investigators is the best assurance of the safety of human subjects. Despite many differences in cultural, ethnic, and national beliefs, physicians the world over are united, as few other humans are. Theirs is a common commitment to the welfare of the sick. It is this commitment that transcends cultural differences.

This commitment can be found in the medical codes and ethics of every major civilization and dating from the earliest times. The Hippocratic, Judaic, Christian, Moslem, Indian and Chinese medical codes all center on the patient's welfare. Benevolence and beneficence are the two universal and unarguable first principles of medical ethics. Starting with these as the foundation, the possibilities of world-wide agreement on principles like those proposed by CIOMS are extremely good.

One thing that will accelerate and facilitate the transcultural dialogue and international agreement is an education in the ethics of clinical investigation. Biomedical ethics is now enjoying world-wide renaissance. The time has never been more propitious for an internal dialogue.

I would like to suggest some ways that education in ethics can be best pursued. I will draw on my personal experiences over the last thirty years in teaching this subject, conducting ethical rounds, and discussing ethical issues with colleagues from every part of the world.

First of all, education in ethics must be more formal, disciplined and organized that in the past. The field is now more complex than ever. Ethical problems and challenges never faced before appear daily. The literature is growing at an extraordinary rate. For example, more than 2,500 articles appeared in English alone last year. Moreover, ethical issues are now being addressed in a sophisticated way by professional ethicists, philosophers and theologians. The physician is no longer the automatic expert on ethical questions. Institutional ethics committees, government commissions, professional associations all now issue statements on biomedical ethical questions.

As a result, physicians must have a knowledge of the methods, content and literature of the new field. They must be able to enter into intelligent dialogue with ethicists, policy-makers, and administrators as well as the general public. They must be knowledgeable and can no longer rely on their technical authority alone. They must realize that ethics is a genuine discipline and a branch of philosophy. It can be taught like any other discipline. Ignorance of ethics imperils the care of the patient and experimental subjects.

Society will be loathe to entrust such an important and perilous undertaking as human experimentation to investigators who are unaware of the complexities of ethical decisions and ignorant of how to make such decisions intelligently. I would go so far as to say that today, and in the future, an education in the skills and methods of ethics -- for both practitioners and educators is as important as a knowledge of anatomy or biochemistry.

Second, the objectives of teaching in ethics must be modest. We cannot hope to make every investigator an ethicist nor would that be desirable. Rather, the objectives should be these: (1) to enable the physician to identify an ethical issue and problem and the moral principles at issue and make an ethical decision; (2) to understand the meaning of the terms used in the ethical discourse, the logic of ethical arguments, and the nature of the presuppositions upon which the argument is built; (3) to understand one's own moral values, their origins and the way they intersect with those of others. Only in this way can the investigator know when he may compromise and when he must not do so. (4) to raise the general ethical sensitivity of clinical scientists so that they can accurately discern the ethical nuances in their work.

These objectives are especially important in our world society where there are so many differing value systems. If the CIOMS and other guidelines are to be accepted globally, they must be based in some common educational core that facilitates transcultural dialogue without compromising deeply held moral values. Different cultures hold different conceptions of the physician patient relationship. They interpret the major principles of medical ethics -- beneficence, autonomy and justice differently; they use different ethical theories and most significantly, they differ in what they accept as the ultimate sources of morality -- medical or otherwise.

The emphasis must therefore be on what is common to call physicians. This is what might be called the "internal morality" of medicine, the set of principles which place the welfare of the patient (or the experimental subject) at the center of the physician's ethical concerns. This is the moral center of medicine and medical science and it cuts across cultural boundaries.

Third, the method of teaching must be based in concrete cases, practical problems and actual dilemmas encountered in everyday practice. Abstract discussions of philosophical ethics have enjoyed little success in medical school teaching of ethics. Moreover, there is a certain antipathy among physicians and medical students to non-empirical, non-quantifiable subjects like ethics. This arises out of the positivist orientation of medical school teaching. However, this obstacle can be overcome if ethics is taught as a discipline, with its own method, literature and content and its relevance to the clinician's and scientist's work made clear.

Finally, we must not have unrealistic expectations of what an education in ethics can achieve. It will not automatically assure that those who take courses in ethics will be virtuous. There is always a gap between knowing what the right thing is, and doing the right thing. But if clinical investigators learn something of the methods and skills of ethics, if they engage in ethical discourse, if they become aware of their own ethical values, the probability that they will make better ethical decisions is increased. This is all that can be hoped from any educational program -- ethical or scientific.

There is encouragement in the development of interest in biomedical ethics now evident in almost every advanced country. Centers of bio-medical ethics are springing up everywhere. Scholars in every country are examining ethical issues. Medical students and physicians are studying ethical issues seriously. Clinical journals now frequently publish articles in ethics. World conferences, and seminars are now so ubiquitous that no one could possibly attend all of them.

The transcultural exploration of ethical issues is well underway in the conferences sponsored by CIOMS in Athens, the Netherlands, and Bangkok. The CIOMS guidelines and this "Summit" conference further attest to the validity of biomedical ethical concerns and the probability of acceptance of a common set of principles to guide human experimentation. The results of all this effort will be greater protection for human subjects and in the long run, more valid research and greater public support for an enterprise so essential to medical progress and human welfare.

Document 12

THE SELECTION OF RESEARCH TOPICS AND THE EFFECTIVENESS OF DIRECTED RESEARCH FOR INTERNATIONAL NEEDS
LE CHOIX DES PROJETS DE RECHERCHE ET LA RECHERCHE DIRIGEE EN REPONSE A DES BESOINS INTERNATIONAUX

José Barzelatto

Discussion: Henri Bricaire

Session H / Séance H

International Summit Conference on Bioethics
Colloque international de bioéthique

The Selection of Research Topics and the Effectiveness of Directed Research for International Needs

PRESENTATION: José Barzelatto

ABSTRACT

It is customary for the choice of biomedical research topic to involve different levels of decision making; that is, from general policies at the government, programme and institutional levels, to the preparation of a protocol and its approval by technical and ethical review mechanisms and the execution of the project through collaboration between the research team and the research subjects.

At all these levels, complex ethical issues arise which affect the rights of society as a whole, particular groups, communities and persons.

An analysis of these complex relationships will be presented, based on the author's personal experience in the management of national and international research programmes, especially the WHO Special Programmes of Research, Development and Research Training in Human Reproduction (HRP). Although the basic issues are the same, in terms of ethical issues international research programmes, such as the WHO Special Programme, represent a higher level of complexity than national programmes, since in a global context they have to cater for different needs and accommodate different value systems. The author believes that the example used to illustrate the above points are generally valid for national programmes.

INTRODUCTION

The excellent general background paper for this Conference prepared by Judith Miller (1), as well as those submitted for discussion, set the scene most appropriately for my presentation on the ethical implications of the choice of topics for research and the effectiveness of directed research for international needs.

I have chosen to describe the World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction because it offers a practical example for most of the issues raised at this Conference. Furthermore, this choice can be justified for the following reasons:

First, the work of the Special Programme covers an extremely sensitive and controversial field which also includes research directed to the medical termination of pregnancy. This was considered "an issue that is dependant upon national legislation and religious and cultural precepts and, therefore, does not lend itself to an international recommendation" in the Proposed International Guidelines for Biomedical Research Involving Human Subjects endorsed by the World Health Organisation (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) (2). This statement, albeit a correct reflection of the state of a controversial subject at the time, is not very helpful today as many research issues involving human subjects present the same criteria. Perhaps more important, recent progress in the field of human reproduction, namely the synthesis of progesterone antagonists, has blurred the distinction between "late contraception" and "early abortion" (3). The WHO Special Programme of Research, Development and Research Training in Human Reproduction conducts this type of research in countries where medical termination of pregnancy is legal and where governments and scientists have expressed an interest in participating in such studies because they believe that safety of induced abortion is a public health factor of considerable significance. In order to support these studies, the Special Programme only uses funds provided by governments that recognize the importance of this type of research for improving reproductive health of women.

This example from human reproduction research illustrates more dramatically the tensions between the rights and responsibilities of individuals (couples in this case) and those of society than possibly any other field of biomedical research. However, there are a multitude of similar, perhaps less dramatic, ethical issues that confront the selection of important research topics in different fields and at various levels of decision making.

Second, the Special Programme is a good example in that it is a truly global programme. To date, scientists and institutions in 85 countries have participated in research projects sponsored by the Programme. The consequent involvement of such a great variety of cultures, religions and political systems has provided a particularly complex perspective to the balance between the principles of autonomy and beneficence, emphasizing again the need for consensus and mutual respect in order to deal peacefully and efficiently with competing moral view points (4).

Third, research on and development of improved and safe new contraceptive methods - an important part of the Programme's activities - are resulting in the introduction of completely new forms of intervention in the reproductive process and in new explanations of the mechanisms of action of existing methods. Individuals and societies are therefore required to take a fresh look at the consequent ethical concepts and implications. Examples of new forms of intervention are the progesterone antagonists and the anti-fertility vaccine. The mechanism of action of intrauterine devices, that was believed to interfere mainly with implantation, now seems to be mainly through interference with fertilization (5).

Finally, the Special Programme is comprehensive and large enough to incorporate activities that represent three different decision-making levels in biomedical research, all of which have ethical implications of a different nature:

(1) The "society and government" level at which decisions relate to what should be done and at which level the ethical concerns are about policies, priorities, prerequisites, relevance to society, etc.

(2) The "professional" level at which decisions relate to what can be done and at which level the main ethical concerns relate to research projects and include the quality and feasibility of the research as well as the expected effect on relatively small population groups.

(3) The "researcher" level at which decisions relate to how to do it and where the interplay between the investigator and the person that is the subject of the research dominate the ethical concerns.

THE WHO SPECIAL PROGRAMME IN HUMAN REPRODUCTION

So as adequately to provide for the above, the Special Programme has a complex structure. It has a governing body, the Policy and Coordination Advisory Committee (PCAC)*, that represents the "society and government" level. It also has a technical body, the Scientific and Technical Advisory Group (STAG), that advises PCAC on technical matters and evaluates the activities of the Programme, thus representing the inter-phase between the "society and government" level and the "professional" level and at the same time providing general guidance to the "professional level" through a systematic evaluation of the Programme's activities. The "professional" level of the Programme is made up of twelve operational committees (the Review Group, the Toxicology Group, nine Task Force Steering Committees and the Committee on Resources for Research) and the responsible leadership of national research centres (close to 200 in 1986) that carry out research projects funded by the Programme. The scientists conducting these research projects represent the third level, "the researcher", of decision making and ethical concerns.

Policy and Coordination Advisory Committee (PCAC)

PCAC's main responsibilities include deciding on general policies and priorities and approving the Programme's budget. Its membership consists of four categories made up as follows:

- Category (a): the twelve largest financial contributors to the Programme (voluntary contributions finance 98% of the budget),

- Category (b): twelve governments elected by the WHO Regional Committees,

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* Although, formally, PCAC has an advisory role to the Director-General of the World Health Organisation, its composition and the mechanisms that support it make it, in practical terms, a governing body. However, it is expected that PCAC will become a formal governing body of the Special Programme on approval of the proposal that it become an inter-agency programme. In this event, the Programme would be co-sponsored by the United Nations Development Programme (UNDP), the United Nations Fund for Population Activities (UNFPA), the World Bank and the World Health Organisation (WHO). WHO would become the Executing Agency and PCAC would then be called the Policy and Coordination Committee (PCC). (Note that, subsequent to the conference, this cosponsorship has been approved.)

- Category (c): three members elected by PCAC, and
- Category (d): three international agencies collaborating with the Programme.

The composition of PCAC in 1987, by category and in alphabetical order, is as follows:

Category (a)

Australia
China
Denmark
Finland
France
Germany, Federal Republic of
Mexico
Netherlands
Nigeria
Norway
Sweden
United Kingdom

Category (b)

Argentina
Bangladesh
Gabon
Indonesia
Kenya
Korea, Republic of
Nepal
Singapore
Tunisia
Turkey
USA
Viet Nam

Category (c)

Ethiopia
Pakistan
Zimbabwe

Category (d)

IPPF **
UNFPA
World Bank

At this level, numerous ethical questions could be raised with respect to decision making and the choice of topics for research. Let us explore those that have to do with the principle of beneficence in an international context and which require that the benefits be perceived by the recipients as true benefits rather than a value system imposed by the donor:

- In the first place, why human reproduction and why WHO? A political decision was taken by a few "leaders" who had society's authority to argue that research on fertility regulation (including contraception and infertility problems) was justified both in terms of Health and of Development. With the provision of new, safe and improved methods of fertility regulation, quality of life could be improved, especially in developing countries. During its fifteen years of operation, the Programme has accumulated scientific evidence to indicate that the need for improved methods of fertility regulation is an essential component of maternal and child health. Indeed, there is also a growing consensus that family planning is an important aspect of the multifaceted strategy that developing countries must adopt, regardless of demographic policies, in order to accelerate

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** International Planned Parenthood Federation.

their development. More recently, the trend set by the private pharmaceutical industry to withdraw from this field of research as increasing liability problems make it unprofitable, further justifies the activities of public sector programmes in the field.

- But why an international effort? Because of the unique sensitivities faced and the controversial nature of the subject which are aggravated by the fact that the main responsibility for financing programmes such as the Special Programme necessarily lie with a few rich countries whereas the benefits are intended mainly to serve developing countries. A politically neutral mechanism with voluntary participation still seems to be the best option.

- Given the emphasis on developing countries, the additional question that naturally follows is whether or not developing countries are fully involved at all levels of decision making in the Special Programme and whether or not their interests (as viewed by them) are adequately taken into account.

In 1987, developing countries represented the majority of PCAC's members (17 out of 30 members). Of the 16 countries that are financial contributors in the 1986-87 biennium, 7 are developing countries. In 1987, there are 153 scientists involved in the work of the 13 operational committees of the Special Programme and of these, the majority (52%), are from 32 developing countries.

The mandate of the Special Programme explicitly states that all activities should be oriented towards the needs of developing countries, a guideline that is strictly followed. Two-thirds of the Programme's operational budget is devoted to the direct support of research projects; one-third is dedicated to assisting developing countries in achieving self-reliance in research. This assistance is achieved by awarding institutional support (equipment, supplies, etc.) and standardization of laboratory procedures through training, provision of matched reagents and an external quality control scheme. At present approximately 70% of the total operational budget is allocated to funding scientists from and working in developing countries (69% in 1985 and 68% in 1986).

Scientific and Technical Advisory Group (STAG)

PCAC makes policy and budgetary decisions guided technically by STAG, a group of 15 to 18 independent and knowledgeable scientists from all over the world representative of different disciplines and who do not participate in any other activities of the Programme's. They meet annually to review the strategic plans of the different components of the Programme, analyse their technical feasibility, advise PCAC on priorities and to evaluate systematically the activities of the different Programme components. In summary, STAG has a dual function: to act between the "society and government" level and the "professional" level of choice and decision making and to evaluate the strategy and activities of the Programme.

This dual role implies that STAG has to face fundamental ethical issues in the choice of research topics to be pursued in the context of an international effort oriented towards the needs of developing countries: priorities need to represent the best possible cost/benefit ratio by focusing the Programme on what is possible in the areas of greatest need, on what is not being done by other programmes, and by ensuring an optimal quality. This role implies not only evaluating systematically and in-depth what the Programme is doing, but also analyzing what others are doing and ensuring that the Programme takes a worldwide role in initiating, facilitating, evaluating and coordinating research and development in what I consider a vital field of interest.

An appropriate example of the kind of ethical issues involved in the choice of research topics is the problem of continued research on Depo-Provera. There has been a heated (and not always scientific) debate about this drug throughout the mass media and worldwide. The debate has emphasized that the Drug Regulatory Authority of the drug's country of origin (the Food and Drug Administration of the USA) refused the registration of this drug for contraceptive purposes as a result of the animal studies. The ethical dilemma exposed is that there is no such thing as 100% certainty. The different levels of decision making in the Programme agreed that the risk/benefit ratio was strongly in favour of Depo-Provera and to date all follow-up human studies conducted by the Programme worldwide provide affirmative evidence in favour of this view. The Programme, therefore, continues to support and conduct research on Depo-Provera, inspite of the continued controversy about the drug in certain countries.

The research topics currently pursued by the Special Programme are reflected in the titles of the Task Forces established by STAG (6). In order of priority these Task Forces are:

- Safety and Efficacy of Fertility Regulating Methods
- Behavioural and Social Determinants of Fertility Regulation
- Long-Acting Systemic Methods for Fertility Regulation
- Post-ovulatory Methods for Fertility Regulation
- Vaccines for Fertility Regulation

- Methods for the Regulation of Male Fertility
- Prevention and Management of Infertility
- Methods for the Natural Regulation of Fertility
- Plants for Fertility Regulation

The fields chosen and the order of priority reflect both PCAC's policy consensus and the pragmatic technical assessment of STAG on what can be done best by WHO within the approved budget.

The first two Task Forces represent concerns for developing countries and guidance of government policies:

(a) scientifically documented safety/efficacy (risk/benefit) ratios for methods in different parts of the world are studied in order to find out whether observations made in developed countries can or cannot be extrapolated to other population groups, and

(b) the analysis of social, cultural, economic, psychological and other factors that influence the acceptance and continued use of fertility regulating methods is made.

Both Task Forces also represent research areas to which WHO has a unique possibility of contributing through its access to worldwide comparative data.

Six of the Task Forces deal with developing new and improved methods of contraception. The Task Force on the Prevention and Management of Infertility deals mainly with appropriate methodology for diagnosis of the causes of this important clinical problem as well as with its prevention and management, again with particular emphasis on the needs of developing countries. The priority rating among these Task Forces reflects mainly the technical feasibility of achieving results as rapidly as possible according to the present state of knowledge, excluding research topics adequately covered by other sources of funding and of relatively less importance to developing countries (i.e. *in vitro* fertilization).

Programme Committees Involved at the Project Level

The Special Programme is run by the international scientific community interested in human reproduction. I have already commented on the composition and role of STAG. The operational components of the Programme are also run by active scientists. The Research and Development component is made up of the different Task Forces, each with its own Steering Committee. The latter are responsible for keeping the Programme up-to-date on progress in research in the specific area to which they are assigned, for maintaining an updated strategic plan which defines specific research lines for the Programme to follow, for eliciting and receiving project proposals within these research lines and for approving proposed projects on the basis of quality and relevance. The membership of the Steering Committees is truly international, and of the 102 scientists presently constituting these committees 55% are from developing countries and 29% are women.

In view of the involvement of Steering Committee members in the research effort of their Task Force, all projects have a peer review by the Review Group, an independent group of scientists. Clinical research projects utilizing new drugs are assessed by yet another group, the Toxicology Group. This double review system is designed to comply with the basic ethical requirement of an independent technical review to ensure quality and feasibility of each project.

The Task Force Steering Committee, the Review Group and the Toxicology Group all share the ethical review of projects. In addition, projects involving human subjects must comply with a general WHO requirement before being funded and be approved by a special ethical review committee, the Secretariat Committee of Research Involving Human Subjects (SCRIHS). This Committee handles more general ethical issues, including legal aspects; its membership consists of WHO staff members (excluding Special Programme staff members).

Furthermore, all projects submitted to the Special Programme must show evidence of approval by institutional and national ethical review mechanisms in order to be considered by the Programme. In fact, in countries where no such review mechanism exists, the Programme has made it mandatory to create an ethical committee at the institutional level and has guided institutions in deciding the constitution with the proper inclusion of non-medically qualified participants. In some developing countries this requirement has resulted in committees that review all research projects involving human subjects from the institutions, even those not supported by WHO, and in some countries these committees have formed the basis for a national system of ethical review.

The ethical review of projects focuses particularly on informed consent and confidentiality. Informed consent forms are carefully evaluated, but in recognition of the limitations of this key procedure in some developing country populations, the special recommendations of the WHO/CIOMS Proposed International Guidelines are strictly followed (2).

Let me illustrate how these different committees interact on ethical issues. After fifteen years, it is not surprising that the majority of projects approved by Task Force Steering Committees are subsequently approved by the other review committees, though, in the case of ethical approval by the Review Group, this has to be unanimous. During the past decade, tacit guidelines have been agreed upon by the different committees. These include severe restrictions on the use of incentives to volunteers other than reimbursement of transport expenses or loss of income. Particular care is given to control groups and the use of placebos is usually not permitted; protocols are designed to compare a new method with an established one, even if this rule makes it at times difficult to interpret results. In early clinical trials, safety issues are resolved before efficacy is tested (i.e. a new contraceptive steroid will be tested initially in women who are sterilized or protected by another method).

Last, but not least, each approved protocol must state preset termination indices in terms of contraceptive failures and the frequency of side-effects. These are carefully monitored at WHO Headquarters and, if such indices are reached, the study is terminated prematurely. For instance, when a long-acting injectable preparation, norethisterone enanthate (NET-EN), was compared with Depo-Provera in a multicentre study as a three-monthly injectable, the study had to be terminated because the preset termination index for contraceptive failure was reached in the former group. The data suggested that the duration of effect of NET-EN is two, rather than three, months. Subsequent large-scale studies conducted, i.e. in India, revealed that NET-EN is a suitable two-monthly injectable.

In addition to a tacit agreement on certain ethical ground rules, committees also consult each other on difficult ethical issues before finalizing certain protocols. For example, it is always difficult to decide on how much animal research and formal toxicology testing is required before a new compound can be administered to human beings. Well in advance of starting a clinical trial, Task Force Steering Committees frequently seek guidance from the Toxicology Group on how to proceed in this respect. Needless to say, animal experimentation is also subject to a number of ethical considerations (7).

Despite an established consensus and frequent consultations resulting in final approval of most projects submitted, it is reassuring that requests for further clarification and amendments are still quite frequent. Systematic renewal of Steering Committee membership probably helps to keep a lively concern for ethical issues.

The fact that contraceptives are intended for use by large numbers of mainly healthy individuals during prolonged periods of their reproductive lives requires particularly strict criteria and guidelines to assess properly the balance of risks and benefits to justify their use. In particular, rare side-effects, either beneficial or undesirable but of public health significance, cannot be assessed until many thousands of healthy subjects have used the method over a substantial period of time. The main point to be emphasized is that growing numbers of experimental subjects must be involved before registration of a new product can be requested and, perhaps more important, that after the product is on the market it would be unethical not to continue the follow-up of the subjects who had used it. WHO recommends to governments that, in future, the submission of a plan to this effect should be a requirement for registration (8). If this practice had been followed in the past, we would perhaps not be debating today, after 25 years of use by 100 million women, whether or not the contraceptive pill increases the risk of certain genital cancers (e.g. cervical cancer) even though it has been established that it significantly decreases the risk of other cancers (e.g. ovarian and endometrial cancers).

ACHIEVEMENTS OF THE SPECIAL PROGRAMME

Since the Special Programme was established in 1972 it has developed for biomedical research a worldwide network of centres collaborating in a global research and development effort to facilitate and improve the conduct of clinical studies of fertility regulation and infertility. The concept of multicentered research teams has evolved into a unique multinational and multidisciplinary collaborating mechanism - the Task Forces - which, together with the network of centres, constitute the backbone of the Programme's activities in research and development. A detailed review of the first fifteen years' activities was recently published in Contraception (9). So far, the Programme has conducted more than 180 multicentred trials involving approximately 185,000 subjects in 150 clinical centres in 53 countries.

One of the two main objectives of the Programme is to increase, through research, access to new and improved methods of fertility regulation that are safe, effective, cost-effective and acceptable. Fifteen years is too short to have reached this goal, especially since we now know that the development of a new contraceptive agent usually takes more than 15 years before it can be put on the market. Nevertheless, I can summarize the progress that has been made and say that the Programme has developed a variety of new fertility regulating methods that are expected to be available to family planning programmes by the dates indicated below:

Year	Product
1988	Two new "once-a-month" injectable contraceptives
	A levonorgestrel-releasing vaginal ring of three months' duration
1991	A three-monthly injectable progestogen
1992	A single biodegradable implant releasing levonorgestrel with an expected lifetime of two years
1994	A sequential antiprogestin/prostaglandin combination for post-ovulatory fertility regulation
	An injectible androgen/progestogen contraceptive for men
After 1995	An anti-hCG "birth control" vaccine.

The second main objective of the Special Programme is to promote and support national self-reliance in human reproduction research in developing countries through institutional development, including research training. The global network of centres collaborating with the Programme includes a majority of centres located in developing countries. Most of these centres could not have participated if they had not received institutional and research training grants. Indeed, some of them were supported by the Programme from their earliest stages of development. During its 15 years of existence, the Programme has provided Research Training Grants and Visiting Scientists Grants to more than 1000 scientists from 60 countries and more than 90% of these grants went to developing country scientists. So far, the programme has spent nearly US$30 million on providing equipment, reagents and supplies to institutions located predominantly in developing countries.

Periodic external evaluations of the Programme on the whole have been supportive of the progress made, while at the same time indicating which areas should be given lower priority. The fact that other agencies within the United Nations system are considering cosponsoring the special Programme and that pledges for 1987 have reached the highest level in the Programme's history (estimated income for 1987 is US$21 million) demonstrates confidence in the progress made and in the future of the Programme. Furthermore, it shows support for the direction of the Programme has taken in this sensitive field of research, including respect for the complex ethical issues involved.

CONCLUSIONS

The operations and the complex structure of an international programme of directed research have been presented with a focus on some of the issues involved in the selection of research topics and in the implementation of research projects. I hope I have been able to demonstrate that, despite the great complexity of the ethical issues faced and the complex operations of the WHO Special Programme, it is possible to manage these issues satisfactorily and to make progress towards our main objective: to improve the human condition.

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DISCUSSION: Henri Bricaire

Dr. José Barzelatto de l'OMS nous a très clairement exposé à l'occasion d'exemples vécus le protocole mais aussi les difficultés pour mener à bien une recherche et d'en prévoir la destinée, et ceci malgré un but bien précisé et noble, un protocole solide et rigoureux, une visée humanitaire. Le message transmis par ce rapport est, me semble-t-il, de souhaiter renforcer dans le futur les vertus de la recherche par une alliance de pensées, de moyens et de règles à l'échelon multinational et même, si possible, mondial.

Il n'est pas dans mon propos de faire l'exégèse de ce travail. Je me bornerai à dégager certaines idées qui en découlent et qui peuvent prêter matière à réflexions et à discussion. Ces idées sont des redites car elles ont été plusieurs fois évoquées dans ce colloque; je m'en excuse. Il faut bien reconnaître que les obstacles rencontrés sont le plus souvent d'ordre éthique, alors même cette éthique varie en fonction de multiples paramètres d'ordre ethnique, national, philosophique et économique.

Comme il a déjà été dit lors de notre réunion, le meilleur commun dénominateur des diverses positions éthiques réside dans les règles fixées dans le code des droits de l'homme bien proches de celles de notre serment d'Hippocrate. Permettez-moi de rappeler que la nation française les a solenellement reconnues dès le 26 août 1789, au lendemain de la proclamation de la République et placées en tête de la constitution de 1791. Ces droits nous paraissent bien résumer buts et limites idéales de la recherche.

Article 2 - Liberté, sécurité.

Article 3 - Souveraineté de la nation.

Article 4 - Ne faire que ce qui ne nuit pas aux autres.
Egalité de tous.

Pourtant ces principes, tout en étant reconnus, ne sont pas toujours respectés. En effet à toutes ses étapes la recherche se heurte dans l'approche du but fixé à des frontières ou des barrages plus ou moins franchissables.

Certes les règles qui doivent être respectées dans un protocole idéal sont clairement définies: consentement éclairé, étapes d'essai successives et sécurisantes, propos humanitaires. Mais, nous l'avons vu tout au long de ce colloque, ces règles sont-elles toujours possibles à suivre ou à respecter? Ne sont-elles point à propices à contournement? Pareil problèmes se posent très souvent à nous autres médecins-cliniciens.

Par contre le choix des sujets de recherche est abondant et varié. Il peut être imposé par de multiples préoccupations, dont nous ne mentionnerons que les principales:

1) En premier lieu préoccupation humanitaire à l'échelon de l'individu. Ce sont les plus fréquentes. Elles peuvent avoir plusieurs cibles:

- possession de nouveaux médicaments, soit curateurs, atteignant le mal à sa racine, soit symptomatiques, améliorant le confort, voire l'espérance de vie d'un patient.

- appréciation de la tolérance d'une drogue ou de certains produits diététiques.

- une mise au point, pour le diagnostic ou la détection de certaines affections, de tests particuliers.

Il est à rappeler à cette occasion la quasi nécessité d'un recours à des sujets de référence sains, voire même à l'auto-expérimentation.

Enfin plus rarement, chez l'homme, étude fondamentale avec le propos de perfectionner nos connaissances en biologie et physiologie.

2) En deuxième lieu, ce peut être une préoccupation d'ordre humanitaire tendant non plus au bien-être d'un individu, mais à celui de la collectivité ou des collectivités, voire de l'univers. Ce sont, à l'évidence, les plus généreuses dans leur inspiraton, mais les plus difficiles dans leur réalisation, mais en revanche elles sont communes à tous les chercheurs, quelle qu'en soit la nationalité.

Largement ouverte, cette voie possède encore de brillantes perspectives. Deux exemples:

- Celui, toujours actuel des vaccinations, en plein essor actuellement avec la découverte du vaccin contre l'hépatite B, les projets de vaccination du paludisme et du SIDA.

- Deuxième exemple, plus futuriste, celui des expériences de cytogénétique, dont il est difficile de définir encore les limites.

A ces projets cependant des limites, hélas, sont souvent vite imposées. Celles-ci sont d'essences diverses.

- Limites matérielles: le coût de la recherche

Cet obstacle ne doit être que relatif et mesuré à l'importance du risque combattu par la découverte. Une maladie très grave justifiera parfaitement un coût élevé; une maladie bénigne possédant déjà des thérapeutiques ne méritera pas un tel engagement. Un exemple, la fécondation artificielle simple coûte environ 15000 francs; l'obtention d'une fécondation "in utero" peut varier de 300000 à 500000 francs, chiffres énormes, devant être cependant pris en considération en fonction de l'énorme retentissement psychologique sur la patiente et son conjoint et sur le coût également fort élevé d'autres méthodes visant à combattre la stérilité ou à contrôler une grossesse à risque.

- D'autres limites sont imposées, cette fois par une nécessaire sécurité, dont nous rappelons les principales:

1) Une équipe de chercheurs dûment qualifiés et souvent spécialisés dans la pratique du domaine de recherche concerné.
2) Un protocole classique rigoureux, d'inspiration nettement scientifique et pratique, avec notamment une excellente phase pré-clinique d'essais d'ordre toxicologique et animal.
3) Protection individuelle contre des risques inévitables et imprévisibles par une assurance. C'est là un sujet encore très variable et non satisfaisant en nombreux pays, dont la France.

- Enfin, des frontières peuvent être placées par la nature même de la maladie étudiée (maladie rare et se prêtant difficilement à des conclusions valables, du moins dans l'absolu; témoins difficiles à trouver en raison de certaines contraintes religieuses ou surtout techniques).

En bref, c'est donc bien l'éthique nationale qui endigue, et le plus souvent à juste titre, l'envol de la recherche. C'est ce qui explique également qu'un certain nombre de règles de cette dite éthique sont ignorées ou contournées. Ces manquements peuvent être expliqués par l'importance du but de la recherche, en particulier celui de contrôler une maladie jusqu'alors mortelle ou sans traitement valable.

Ce peut être également le fait d'un terrain psychique particulier des sujets malades ou témoins chez lesquels un consentement éclairé est impossible. Ce peut être enfin les conditions matérielles dûes au lieu d'implantation de la recherche. Il peut en être ainsi de la recherche en collectivité du milieu tropical. Il en est ainsi enfin du fait que l'éthique conduit à des attitudes diverses, en plus ou en moins, sur un même problème, selon le pays où le travail s'effectue. Deux exemples: la fécondation artificielle unanimement reconnue par certaines nations, sévèrement contrôlée par d'autres nations. De même, la cytogénétique actuellement très à l'étude, sans problème pour la prophylaxie et le diagnostic, plus controversée en recherche appliquée future.

On voit donc l'énorme intérêt qu'il y aurait à trouver des règles applicables à l'ensemble de nos collectivités.

A cet égard, les conclusions de notre colloque pourraient être précieuses pour protéger la sécurité et amplifier les processus de recherche.

A l'échelon national, il est peut-être souhaitable de multiplier le nombre des comités d'éthique. Mais il est en tout cas indispensable, du moins dans de nombreux pays, de renforcer leur rôle et leurs pouvoirs de conseil et de surveillance.

A l'échelon individuel, il convient certes de s'assurer de l'intérêt du projet et de la valeur des équipes de recherche. mais aussi et surtout, il convient de prévoir et d'assurer une protection civile et, si possible pénale, des patients mais aussi des chercheurs contre les risques encourus par cette même recherche.

Mais c'est surtout à l'échelon multinational et international que doivent se concentrer les efforts de perfectionnement.

Par des réunions telles que celle-ci, en recherchant une unification aussi complète que faire se peut, de nos règles et de nos protocoles.

Par des incitations économiques et financières aussi généreuses que faire ce peu mais surtout réparties harmonieusement et équitablement. Cette solidarité des riches ou des moins riches n'est-elle pas un des fondements les plus nobles de l'éthique entrevue dans son sens très général et le plus noble?

Ces idées sont d'ailleurs concrétisées par les questions énoncées sur notre programme qui engagent la discussion.

Document 13

THE TRANSFERABILITY OF SYSTEMS OF ETHICS REVIEW
LA TRANSFERABILITE DES SYSTEMES D'EXAMEN ETHIQUE

Jean Michaud

Discussion: Koichi Bai

Session J / Séance J

International Summit Conference on Bioethics
Colloque international de bioéthique

La transférabilité des systèmes d'examen éthique

PRESENTATION: Jean Michaud

Résumé de l'exposé sur la transférabilité des systèmes d'examen d'éthique

Préambule:

On constate une tendance à la recherche d'une meilleure communication et d'une certaine harmonisation entre états. En fait, les ressortissants des états voyagent de plus en plus. En droit les exemples ne manquent pas, citons le Marché commun européen, les traités multilatéraux tendant à l'unification des règles de droit.

Première partie: Le mouvement d'unification peut-il s'appliquer à l'éthique?

a) Cette extension connaîtrait deux obstacles: (1) Les principes d'éthique s'accommodent mal des textes; (2) Les principes d'éthique varient selon les états.

b) Cette extension présenterait deux avantages: (1) Une meilleure compréhension entre les hommes; (2) Une meilleure efficacité de l'éthique à l'intérieur de chaque état, par exemple, les essais de médicaments sur l'homme prohibés dans un état sont pratiqués par les ressortissants de cet état dans un autre état.

Deuxième partie: Les instruments à utiliser

a) Sur le plan international.

Déclarations de Nuremberg, Helsinki, Tokyo, etc.

b) Sur le plan national.

Travaux du comité consultatif national d'éthique français. Rapport Warnock, Rapport Benda, etc.

Troisième partie: L'énoncé de quelques principes éthiques fondamentaux qui pourraient devenir communs au regarde de la recherche sur les humains.

a) Sur le plan de la protection des sujets. (1) Dignité de l'homme; (2) Non-commercialisation du corps humain; (3) Modalités du comportement du sujet.

b) Sur le plan des progrès à espérer. (1) Développement de la notion de solidarité entre les hommes; (2) Développement de la notion de participation active des sujets à l'expérience par la connaissance de ces modalités et de ces résultats.

Conclusion:

Ces idées doivent faire l'objet d'études approfondies à la fois multinationales et multidisciplinaires. Elles pourront progresser, grâce aux travaux, sous une forme à définir, d'un organisme qui serait créé en vue de l'élaboration de directives en ce sens.

LA TRANSFERABILITE DES SYSTEMES D'EXAMEN ETHIQUE

Valery a écrit une phrase frappante: "l'ère du monde fini commence". Il n'est en effet plus guère de recoins de notre planète où l'homme n'ait pénétré. Arrêtés aux frontières extrêmes il nous reste cependant nombre de découvertes à faire en nous ouvrant les uns aux autres, en essayant de comprendre ceux qui nous sont devenus si proches par la facilité conquise de les atteindre, en essayant de ne plus travailler isolément vers des objectifs parfois égoistes.

Le mouvement a commencé d'abord en fait. Les hommes voyagent, communiquent entre eux de plus en plus. Les relations d'affaires, intellectuelles, touristiques se multiplient. Nous avons franchi de longues distances pour nous trouver ici rassemblés.

Le mouvement s'accomplit aussi en droit. Les traités multilatéraux cherchent dans des domaines précis à uniformiser les législations, ainsi en matière de transports, en matière de propriété, en matière de titres de crédit. Je m'en voudrais de ne pas citer à cet égard le marché commun européen.

Il va de soi que plus les nations sont proches par leur culture, la civilisation dont elles procèdent, les populations qui les composent, plus les rapprochements sont aisés. Moins on pense différemment, mieux on peut penser ensemble.

Dès lors pour les nations qui se sentent entre elles des affinités, qui ont déjà prouvé qu'elles étaient capables de se comprendre, de réagir de même façon devant le même événement, n'y a-t-il pas une voie à explorer, plus noble, que celle du contact entre les individus ou de l'uniformisation des économies ou de certains systèmes juridiques, la voie de l'harmonisation éthique. Entendons-nous bien. Il ne saurait s'agir de l'ambition démesurée et peut être inopportune de construire une morale universelle. Notre propos doit être beaucoup plus modeste pour deux raisons: l'objet de nos travaux est limité aux recherches sur l'homme (et déjà ce domaine est très vaste); les nations ici représentées ne sauraient parler qu'au nom d'une partie de l'humanité.

Mais sur les chemins de l'éthique bio-médicale nous pourrons éventuellement trouver des directions utilisables pour d'autres parcours et ce que nos idéaux ont de commun pourra nous y aider.

Les obstacles à une telle démarche ne sont pas minces. Il y a d'abord la nature même du concept éthique. Il ne se laisse pas facilement traduire. Nous cherchons ensemble à déterminer, au point où nous en sommes arrivés, si sur quelques points de portée capitale il est possible d'envisager une poursuite de la réflexion en vue de la mise au point d'une formulation commune.

Mais il faut bien voir que nous ne sommes pas dans le domaine de la Loi qui décrit, impose, sanctionne. Nous sommes dans celui de la morale (n'ayons crainte du mot) qui soustend ou entoure la loi, parfois la précède, parfois lui reste étrangère (elles ont même centre et non même circonférence, disait Bentham) et qui surtout incite et tend à persuader mais n'oblige pas, du moins temporellement. Il n'existe pas beaucoup de codes nationaux d'éthique. N'est-ce donc pas une entreprise démesurée que de déployer des efforts en vue d'élaborer, non pas même un chapitre d'un code éthique international, mais seulement des éléments de ce chapitre.

On voit donc ainsi la différence qui apparait avec les traités multilatéraux trouvant une matière à exploiter dans les textes nationaux.

Telle est la première difficulté.

Il en est une seconde. Mais son existence même invite à la vaincre. Elle résulte de la diversité des principes éthiques selon les Etats. Or cette diversité peut apparaître comme un inconvénient ou peut être même un mal que nous avons précisement pour tache de réduire.

Quoiqu'il en soit, malgré nos points communs, malgré certaines des aspirations fondamentales qui nous unissent, nous connaissons des divergences de pensée, de conceptions. Nous sommes plus ou moins en retrait ou en avance les uns par rapport aux autres (si l'on est fondé de parler de degrés en pareille matière) dans le domaine si délicat, si controversé de la recherche sur l'homme. Ce qui pour les uns est progrès, peut être considéré par les autres comme régression. Si le principe même de la recherche est admis, les limites à lui impartir varient selon les fondements et les finalités qu'on lui assigne.

On comprend aisément ces divergences. Il s'agit de l'homme à titre principal, donc de l'idée qu'on a de son rôle en tant que personne et en tant que partie du corps social. Selon qu'une société nationale privilégie l'un ou l'autre de ces éléments, elle influe d'autant sur l'éthique qu'elle proclame.

Les différences sont parfois enrichissantes, sources de progrès. Elles ne le sont plus lorsqu'elles deviennent divergences et facteurs de concurrence. Le glissement du domaine des idées et des principes à celui de l'économie, n'est pas toujours évité.

Nous savons que les expériences sur les humains, qui soulèvent de difficiles problèmes sont loin d'être admises par l'ensemble des nations. Nous savons aussi que sur la voie de la recherche scientifique en matière de nouveaux médicaments ou de thérapeutiques nouvelles, il arrive un moment où seul l'essai sur l'homme est de nature à permettre le franchissement d'une étape, après épuisement de tous travaux en laboratoire et sur l'animal. Quelles sont, ou risquent d'être, les conséquences de cette situation dans un Etat qui prohibe l'essai sur l'homme? Elles peuvent être de deux sortes: le chercheur s'incline, renonce soit qu'il se contraigne à accepter la philosophie de ses concitoyens, soit qu'il partage cette philosophie. Il sait cependant que dans d'autres pays que le sien ces scrupules là n'ont pas cours et que dès lors les progrès s'accompliront ailleurs.

La seconde attitude consiste à réaliser sous d'autres cieux les travaux qu'on ne saurait effectuer dans le pays dont on relève. Le laboratoire fera exécuter hors les frontières certaines phases de l'essai, le savant ira s'installer à l'étranger. C'est l'exode des cerveaux.

Il convient donc d'établir la balance entre les justifications profondes de l'interdit et les inconvénients qui, en résultant, sont à la fois d'ordre scientifique et économique. Peut-on maintenir une position de rigueur, ou le principe peut-il céder de quelque manière ? Mais au delà de cette alternative, il faut constater que la différence selon les nations des normes éthiques, appliquées à ce problème cause préjudice aux plus intransigeants à moins qu'ils n'y échappent par le profit tiré de recherches auxquelles ils n'ont pas participé effectivement.

Il ne s'agit pas dès à présent de marquer une préférence pour un systéme éthique plutôt que pour un autre. Il s'agit seulement de montrer l'intérêt qui s'attacherait à la réduction des différences.

Par conséquent les obstacles ne sont pas négligeables, et les inconvénients à la diversité actuelle ne le sont pas non plus. Mais en regard, des instruments de travail existent qui devraient permettre de réduire les uns et les autres, ou dont l'existence devrait au moins nous encourager à tenter de le faire.

Nombre de nations se livrent depuis quelques années à l'approfondissement de l'éthique. C'est un retour de ce qu'on appelle plus simplement morale sous la poussée des problèmes que font surgir les progrés scientifiques en particulier en matière de biologie et de génétique.

Nous nous contenterons de citer trois exemples. Les deux premiers nous viennent de Grande-Bretagne et de République Fédérale d'Allemagne. Il s'agit respectivement des rapports dits Warnock et Benda. Ils ont le même objet: définir les règles éthiques relatives à la fécondation artificielle. - Il ne s'agit donc pas directement du sujet que nous traitons . -Mais à l'occasion des développements qu'ils comportent, le problème est posé de l'expérimentation sur des êtres humains. Et surtout est posé, le problème beaucoup plus difficile de la définition de la personne humaine. Si l'embryon est déjà une personne, les obstacles à l'expérience surgissent à son propos comme à propos d'une personne arrivée à maturité. Ces réflexions britannique et allemande sont importantes pour nous en ce qu'elles montrent la probable nécessité dans laquelle nous nous trouvons peut être de ne pas limiter notre étude.

L'essai sur l'homme est-il possible au terme d'un consensus dégagé entre nations sur quelques principes? Mais qu'est-ce que l'essai? qu'est-ce que l'homme? je me borne à vous livrer ces questions qui nous amèneront peut être, ou amèneront ceux qui procéderont de nos travaux à s'interroger sur ce qui peut se passer aux deux bouts de la chaine: recherche sur l'embryon (est-ce déjà une personne?) recherche sur l'individu végétatif chronique (est-ce encore une personne?).

De son coté la France a travaillé sur la matière des expériences sur l'humain. A ses débuts notre comité national d'éthique a rendu un avis intitulé: "Avis sur les problèmes éthiques posés par les essais de nouveaux traitements chez l'homme" (Octobre 1983).

La France ne dispose pas d'une législation autorisant de tels essais. Des projets sont en cours d'élaboration. L'avis du comité d'éthique constitue à cet égard une incitation. En effet il ne conclut pas au maintien d'une prohibition. Il admet le principe de l'essai. Mais après une étude approfondie, il fixe des conditions très limitatives. Ce document me parait constituer un élément précieux pour notre propre réflexion, un instrument de progrès en vue du rapprochement des manières de voir de nos différents pays. En tous cas il a marqué, de notre point de vue national, une étape vers la reconnaissance raisonnée de l'essai sur l'homme.

Plus importants encore pour nous apparaissent les documents internationaux dont la mise au point démontre la possibilité d'un accord entre différents pays sur cette matière. Chacun connait les étapes de cette oeuvre accomplie au delà des limites fixées par les frontières: Nuremberg, Helsinki, Tokyo, Manille, avec pour point de départ le souci d'éviter le renouvellement des graves abus commis pendant la guerre, non par une interdiction totale de l'essai, mais par son strict encadrement.

Ces documents internationaux, après l'impulsion donnée par ce qu'on a appelé le code de Nuremberg, émanent soit de l'assemblée médicale mondiale (Helsinki I et II) soit du projet conjoint de l'organisation mondiale de la santé et du conseil des organisations internationales des sciences médicales (Manille). Ils contiennent de précieux éléments qui pourraient servir à l'élaboration d'une doctrine éthique internationale en matière de recherches sur l'homme. Ils témoignent d'un souci commun des représentants des divers états par l'intermédiaire de leurs organisations internationales ou de certaines instances nationales.

Il convient maintenant de se demander si les Etats eux-mêmes en sont arrivés, ou sont en mesure d'arriver à un stade de réflexion suffisant pour prendre compte et dégager un consensus sur un certain nombre de principes. Il va de soi que les déclarations rappelées précédemment étant sur certains points très détaillées très explicites, ne sauraient être reproduites intégralement dans un instrument de plus vaste portée. En revanche il n'est pas exclu, la réflexion ayant progressée, que d'autres principes, d'autres normes puissent être dégagées qui n'étaient pas apparues dans une phase antérieure.

Deux phrases tirées de la déclaration d'Helsinki, devraient orienter notre débat. Les voici: "le progrès de la médecine est fondé sur la recherche qui, en définitive, doit s'appuyer sur l'expérimentation portant sur l'homme", et "le droit du sujet à sauvegarder son intégrité, et sa vie privée doit toujours être respecté."

Ce sont les deux pôles entre lesquels il nous faut évoluer: intérêt de la science, intérêt de l'homme. Ils ne sont pas contradictoires dans la mesure où l'intérêt de la science est aussi à échéance celui de l'homme. Ils le sont dans la mesure où l'intérêt de la science apparait au détriment, dans l'immédiat, de l'intérêt de l'homme.

C'est en fixant notre attention sur chacun de ces impératifs que nous parviendrons à approfondir quelques données d'ordre éthique. Il faut donc parler de protection, puis ensuite de progrès.

La protection de l'homme est imposée par la notion de sa dignité. Il est une fin et non pas un moyen, fut-ce en vue d'une fin empreinte de noblesse. Malgré de dramatiques et épisodiques retours en arrière, voilà une idée qui a fait son chemin au long des siècles et qui va s'affinant de plus en plus. Mais la dignité est menacée chez l'être affaibli; elle l'est par ceux qui disposent de pouvoirs particuliers. Le malade est un être affaibli; le médecin et le chercheur disposent de pouvoirs particuliers. Dès lors l'utilisation d'un sujet comme truchement en vue d'obtenir de meilleures connaissances ou de meilleurs résultats scientifiques ou thérapeutiques, peut être, compte tenu de ces deux facteurs, une atteinte à sa dignité. S'il s'agit d'un patient, il se trouve en état de moindre résistance, et dans tous les cas (patient ou sujet sain) il est dominé par le pouvoir scientifique que représente le technicien de la santé.

Ce n'est là qu'un principe, antérieur à toute application, sur lequel, je le pense, aucune des sociétés que nous représentons n'entend revenir, mais qu'il n'en faut pas moins répéter inlassablement.

Si la dignité est respectée, pourquoi prohiber l'expérimentation sur l'être humain? mais comment respecter la dignité? D'abord en traitant le sujet comme une personne consciente et responsable. Il doit savoir ce qui lui advient. Il doit y consentir. Son accord ne doit être assorti d'aucune espèce de pression. C'est la notion de consentement libre et éclairé qui a déjà été dégagé par les déclarations d'Helsinki et de Tokyo. Cela parait simple mais l'est beaucoup moins qu'on le pourrait croire. En premier lieu qu'en est-il du consentement des enfants? des aliénés? Ensuite le consentement d'un malade peut-il jamais être libre? Jusqu'où peut se prolonger l'information donnée au sujet, lorsqu'il s'agit de renseignements d'ordre scientifique souvent difficiles à comprendre et de nature parfois, par l'effet de mystère qui les entoure, à effrayer exagérément celui qui les reçoit.

On peut trouver un autre exemple d'atteinte à la liberté du sujet si l'argent intervient à l'occasion du processus d'expérimentation. Certes l'individu qui accepte d'être payé pour sa participation à un protocole d'essai, accepte librement. Mais sa liberté de consentir à une atteinte à son intégrité physique ou mentale n'est-elle pas obérée par l'espoir d'en tirer un profit pécuniaire? Ce n'est pas douteux s'il en fait son moyen de vivre, ce l'est davantage s'il en fait un moyen accessoire. Au contraire, le problème ne se pose plus s'il reçoit non pas une rémunération mais une indemnisation en compensation du temps passé ou de l'incommodité ressentie.

Le consentement est également un terrain sur lequel nombre de pays peuvent chercher à définir une position commune à partir du moment où ils y voient une manifestation concrète de la dignité. Il leur restera à définir le contenu de l'adjectif "libre" et les limites acceptables de la lucidité du sujet. Sauront-ils ne pas se diviser sur le problème de la rémunération dont on sait qu'il est actuellement perçu de manières très diverses?

La protection manquerait d'efficacité suffisante si elle n'était organisée ou controlée par une instance extérieure, à la fois aux expérimentateurs et aux sujets. Ainsi se justifie le role des "comités d'appréciation éthique" pour reprendre l'expression utilisée par le document de Manille ou des comités d'éthique, pour reprendre la dénomination française. Ces organismes ont en général pour fonction de formuler un avis sur le caractère éthique du projet d'essai qui leur est soumis. Il ne se dispensent pas pour autant de porter d'abord une appréciation sur l'aspect scientifique faute duquel on n'aurait même plus à poser le problème éthique. Ils présentent un certain degré de multidisciplinarité. Leurs avis ne comportent directement aucune conséquence contraignante.

Il existe déjà des comités d'éthique dans un certain nombre de pays. Ils sont, ou peuvent devenir des lieux de réflexion. En l'absence de dispositions législatives adaptées au domaine de la recherche, qui par nature devance toujours la loi, ils servent de relais temporaires entre le fait et le droit, et peut être même parfois permettent-ils de faire l'économie de quelques textes.

Une recherche que nous ferions à ce propos, viendrait heureusement compléter celle que nous pourrions mener en vue d'une certaine harmonisation des conditions de l'expérimentation. Poser le principe de la nécesaire intervention d'un organisme extérieur, dont les formes pourraient être variables, apportent une garantie protectrice qui serait un gage d'objectivité.

Ce ne sont là que des exemples des points sur lesquels un échange d'idées peut profitablement s'instituer. Il y en a bien d'autres. Mais je n'ai pas eu le sentiment qu'on me demandait d'être exhaustif.

La protection ayant été envisagée, il est temps de parler de progrès, c'est à dire de travaux scientifiques qui tendent, grâce au terrain irremplaçable que l'homme constitue, vers de nouvelles connaissances dont l'ensemble des hommes pourrait tirer avantage.

Quelles est la justification de l'incommodité, de la perte de temps, de la souffrance parfois, du risque qu'accepte de subir le sujet d'expérience, en toute conscience? Nous savons qu'elle ne peut être en règle générale, dans la rémunération. On la trouve d'abord pour un malade, dans l'espoir de recevoir plus tard une thérapeutique améliorée et aussi de coopérer à la guérison, à échéance, des malades de la même catégorie. On le trouve aussi dans un sentiment de plus haute solidarité de la part des sujets sains. Leur motivation peut simplement tenir à la volonté de participer au bien commun. Telle est déjà la détermination du donneur de sang bénévole.

Or il n'est pas inconcevable de faire passer au rang des principes généraux, un message d'une solidarité internationale qui se traduirait par une contribution de chaque homme consentant, à la santé de ses semblables de quelques pays qu'ils relèvent.

Pareil sentiment se trouverait singulièrement renforcé si le rôle du sujet d'expérience faisait l'objet d'une nouvelle réflexion.

Tel qu'actuellement considéré, il est un personnage conscient, concourant à un essai dont il connait les modalités, mais purement passif.

Ne pourrait-on dépasser ce stade?

On a vu que le sujet manifeste sa solidarité avec ses semblables en acceptant de donner ou de prêter, quelque chose de lui-même. Mais si l'on s'en tient là il reste une forte part d'abstraction dans le résultat du geste d'expérience accompli. Au contraire, s'il est renseigné le plus complètement possible non seulement sur ce qui va lui advenir mais aussi sur l'objet de cette expérience, ses modalités, ses perspectives, il en va tout autrement. Il peut en venir à espérer le succès des chercheurs, à se désoler de leur échec. Il n'est plus un être passif livré à de mystérieuses pratiques pour devenir le collaborateur d'un essai auquel il se trouve essentiellement associé. L'information ainsi reçue ne devrait pas cesser à la fin de l'essai; elle serait encore fournie au moment des résultats.

Certes si ce schéma devait trouver ses limites en fonction de la personnalité du sujet et de la complexité de l'essai, il n'en demeure pas moins que dans un certain nombre de cas, il confèrerait au sujet un regain de dignité.

Cette notion qui n'apparait pas dans les textes cités, nécéssiterait un approfondissement. Tout en aidant à l'élaboration d'un consensus entre nations diverses sur l'expérimentation sur l'homme, à l'intérieur de strictes limites, elle permettrait de faire échapper définitivement le sujet d'expérience au statut dégradant de cobaye.

Nous ne saurions je pense, prétendre résoudre ces problèmes pendant notre colloque, nous contentant de les poser dans leurs principales dimensions.

Si cependant nous estimions, et tel est mon avis personel, qu'il faut poursuivre la réflexion, il nous appartiendrait d'émettre un voeu: qu'un organisme à définir, représentant nos nations, soit constitué, qui aurait pour tache de recenser les quelques principes éthiques fondamentaux en matiére de recherches sur l'homme et dont l'énoncé nous permettrait d'assister à l'éclosion des premiers éléments d'un code international d'éthique.

Voici nos réponses aux questions posées par Mme Judith Miller dans le document de travail qu'elle a élaboré, sur le problème qui nous retient présentement.

1. Il y a entre pays des points communs suffisants pour que certaines normes soient exportables.
2. Une importance particulière doit être accordée aux notions de non commercialisation, de consentement, de comités d'éthique.
3. Ce sont là des notions reçues dans différents pays.
4. On peut rechercher d'autres normes, facteurs de rapprochement.
5. Au titre des nouvelles normes on peut retenir la participation active à l'essai en développant la conscience de la solidarité entre les hommes.
6. La constitution d'un organisme serait utile en vue de prolonger cette réflexion.

En conclusion un système complet d'examen éthique ne saurait être actuellement transféré d'un pays à d'autres pays. Mais quelques éléments de ce systéme peuvent subir ce passage, à partir desquels progressivement l'élaboration d'un code international d'éthique pourra être envisagée puis menée à bien.

DISCUSSION: Koichi Bai

1. In thinking about the transferability of systems of ethics review, methodological consideration should be given to international transferability of the points at issue in bioethics in general.

   The most influential view so far on the relationship between universality (internationality) and national particularity places a high value on universality of ethics and a world-wide sharing of a sense of values and strongly insists on directing our efforts to this goal at least.

   There is, however, an opposite view, which emphasizes the particularity of culture and ethos to each nation. The latter view recently has been intensified by certain fields of science, such as cultural anthropology. According to the latter view, universality imposes the advanced Western countries' sense of values on other parts of the world and thus may be regarded as ethical imperialism. Adapted to the problems in Japan, it is also a view stressing what is peculiar to Japan in contrast to Western culture.

2. I would like to take a position slightly different from either of the above views. My sequence of thinking is:

   First, it is necessary to make efforts to comprehend the local perspective on bioethics issues. This must precede comparisons, for example, of Japanese and Western approaches.

   Second, even if this process reveals views in one country which are different from the predominant views of other countries, we should consider that either perspective may be an element of a universal view and not prejudge one as universal because it is predominant in many countries and dismiss another as simply peculiar to one country or culture, such as Japan. In other words, even if view-B is in Japan while view-A is predominant in the other countries considered, it does not follow that A is universal and B is peculiar or specifically Japanese. By eliminating such preconceived notions, we make an effort to regard not only A but also B as two elements of a universal view. In fact, instead of looking upon different ways of thinking as the opposite to the universal one, we should reconsider them as second thoughts about a universal way of thinking which may have been looked upon as self-evident. Thus we cast suspicion on absolute statements of established universality by openly considering local characteristics.

Third, those characteristics which remain peculiar to a nation even after trying every means described above, should continue to receive close observation and thought as to how to reconcile them with the predominant view.

I therefore object to a view which accepts Western thoughts as almighty or absolute and ignores Japanese peculiarities. However, I also object to a view in which Japanese characteristics necessarily dominate.

In other words, I propose a comparative study in detail, accepting local diversity without necessarily presuming its peculiarity but regarding it as another essential element of universality.

The example of Japan used here applies even more strongly to developing countries. The necessity of paying high regard to their peculiarity will become still more pressing.

The foregoing general consideration is not uniform with respect to all issues of bioethics. How can it be applied to the theme with which we are confronted? There may be few regional differences in systems of ethics review; nevertheless, Dr. James Miller[1] once pointed out differences even between America and Canada on the experimentation on children. This impresses me.

My comments have been vague and abstract so far. May I now introduce the following concrete experience to you as one example?

In 1985, Japan changed her policy on "Clinical Trials Conducted in Foreign Countries." According to PAB Notification No. 660 (June 29, 1985),

> Data from clinical trials conducted in foreign countries can be accepted as data for examination so long as such data meet the conditions and requirements specified in III below.
>
> In the case of drugs other than in vitro diagnostic agents, however, data from trials conducted in Japan

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[1] James Miller, Recommendations on Experimentation with Children: Some Differences in Canadian and American Approaches, 2 Bioethics Quarterly 3 (Fall 1980).

> are required, if necessary. Data from clinical trials conducted in Japan shall, in principle, be submitted in the case of tests on absorption, distribution, metabolism and excretion, tests for dose finding and controlled clinical trials.

Since it is beyond my power to evaluate how to access the relative weights of the principle and its exception, it will be difficult for me to be definitive on "The Transferability of Systems of Ethical Review". However, this example may help us think about the problem. Does the acceptance of the result of clinical tests in foreign countries mean that we trust their ethical review? Will it not require occasionally the inspection of the local conditions for clinical tests? The answer to these questions will depend upon to what extent the process and procedure might vary from country to country, especially the specific mode of getting informed consent and doctor's explanations. This brings my discussion back to the starting point. Would you permit me to present such questions in order to promote discussion?

Document 14

POSSIBILITIES FOR REFINEMENT AND EXPANSION OF TRANSNATIONAL STANDARDS
POSSIBILITES DE RAFFINER ET D'ETENDRE LES NORMES TRANSNATIONALES

Abbyann Lynch

Discussion: Gustav-Adolf Martini

Session J / Séance J

International Summit Conference on Bioethics
Colloque international de bioéthique

Possibilities for Refinement and Expansion of Transnational Standards

PRESENTATION: Abbyann Lynch

Mr. Chairman:

It is a great pleasure to be asked to speak at the beginning of the end, although my preference would be to speak at the end of the beginning, given the title I have been assigned.

As noted in the paper originally sent to you under the given title, a listing of areas for possible refinement and expansion as regards transnational standards would certainly include the various items already listed on our agenda. During our meeting these and several other unproposed agenda items have been discussed, with action towards implementation initiated in several cases. While a variety of unanticipated questions has arisen here, many more will undoubtedly surface in our later reflections concerning this group's activity. The problem for this particular speaker, then: at this point in our deliberations, what of value can now be said?

My invitation to speak on the subject announced came with the proviso that I first submit a "holding paper" - already in your hands. This preliminary paper was to be refined during the work of the Conference so that it could become a brief summary of the week's labours cum look towards the future. In making my "second remarks" at this time, I do not wish to repeat what we have already said here, but I do wish to comment on three specific issues I believe to be fundamental to any activity of refinement and expansion of transnational standards as regards the ethics of research using human subjects. (In Canada, we might speak then of this kind of presentation as a 'dog's breakfast': make the best of what is left).

Area # 1 -- Preparing the Ground

In his presentation this morning, Dr. Bai spoke eloquently of our need to respect, as well as to widen and deepen our understanding of, each other's cultures. In attempting to speak jointly about ethics, this is surely a first requirement. Having agreed on that point, we must also agree as to what constitutes ethics: what it is and what it is not - its scope, its mode of operation, its appropriate use and so forth. Unless we have a common understanding about the difference between law and ethics, for example, or of the meaning of various terms like moral reasoning, moral philosophy, morality and ethics, we may well find ourselves in serious difficulty. Further we must have some agreed upon meaning for research experiment, therapy, innovative or novel therapy, and the mixed enterprise of research therapy. The essential first step, then, is one of common definition; lacking this, we cannot hope to derive, much less implement, any transnational research ethics standards.

A second step required is for continuing common research into the ethical aspects of human experimentation. Thus, the ethical dilemmas posed in the discussion of innovative therapy, so well described by Professor Friesen, must be explored, as must the ethical questions arising in the ongoing development of new techniques and of new scientific knowledge. At the same time, attention must also be given to perennial questions like truthfulness, privacy, consent and the loyalty between the practitioner or the investigator and the research subject or patient as these questions arise in novel situations. Research in this area of ethics must be directed proactively, so far as that is possible.

A third step required here is common refinement of the ethics review process. The concept itself has evolved greatly in the short time since Helsinki-Tokyo. The text from the original Helsinki document reads as follows:

> "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance."

The CIOMS document and various national statements have updated this particular Helsinki recommendation. In this meeting, the ethics committee notion has been examined very carefully: how it is to be constituted in terms of membership, mandate, content for examination; how its procedures are to be orderly, fair and efficient; how the committee is to be accountable, creditable, respectful of privacy and the like. If it is the intention of this group that the ethics committee (which had its humble beginnings at Helsinki) be a vehicle which will protect research subjects even as it assists in pursuit of scientific knowledge, if it is the intention that such a committee shall encourage researchers to persist in their work in an ethical manner while the committee also reflects social mores, then much more research is needed so as to uncover what is the present status of these committees. In addition, some carefully-applied ingenuity will be required to suggest appropriate paradigms, adaptable to the various cultures involved in the effort, if the ethics committees are to be successful.

We shall also have to agree as to the principles on which the standards to be applied by our recommended committees are to be based. This was discussed eloquently in this morning's papers and has been a theme in all of our deliberations. Are such standards identical in our various cultures? Could agreement on procedures perhaps substitute for agreement on principles? If there is some conflict among the principles suggested, which are to have priority and how is that to be determined?

In short, if transnational standards are the aim, this conference has set a preliminary agenda towards achieving that aim. In working to realize it, bureaucratization of the ethics committee (it exists to exist, or less reverently, it exists to cause trouble) is to be avoided; at the same time trivialization of ethics - the reach for the "ethical fix" is equally a danger. In the end, the goal is deliberate consideration of ethical questions by the ethical ethics committee.

To conclude comment on this first concern. This group ought to support the notion of on-going investigation as regards:

1) common definition of ethics and terms relevant to the ethics of research;

2) the ethics of research with human subjects; and

3) the ethics committee as the vehicle for application of ethical standards insofar as research with human subjects is concerned.

Area # 2 -- Education and the Research Ethics Enterprise

The germane transnational documents already drafted have a widely-acclaimed goal: the well-being of those human subjects used in the process of furthering scientific advance. Enormous collaborative effort was harnessed towards the phrasing of their carefully-delineated concepts. With the exception of the Helsinki II Guideline regarding non-publication of unethical research, and the possibilities implicit in the recommended review process, however, these statements identify no negative sanction for activity contraindicated by their expressed goal. In other words, these documents have force in the moral order only; their power to bind is restricted to the power of example and persuasion to action. Legislation complementary to the documents exists in certain jurisdictions, but this is not a universal state of affairs.

Given this background, what has the success of the documents been? Are the concepts expressed in them well-known? Are the guidelines followed in practice? There is some reason to be tentative in giving any affirmative response here. Consider the following examples:

a) In their discussion of the WHO/CIOMS project, Drs. Bankowski and Dunne comment on the use of the Guidelines of Nuremberg and Helsinki/Tokyo by respondents to their questionnaire: "The fact that half of the respondents did not use the Helsinki/Tokyo Declaration suggests that they may not be aware of it" (1). The respondents referred to here were from ministries of health and medical faculties in sixty developing countries.

b) Quoting from the same report, "...a very detailed protocol for a double-blind trial on human subjects of the efficacy of a long-acting tetracycline on a rickettsial disease, half of the subjects to receive putatively prophylactic doses of the antibiotic and the other half to receive only a placebo, all subjects being artifically exposed to the disease by the bites of infested vectors. Volunteers for the trial were to be given a "Fact Sheet" informing them inter alia that there was a 'small risk of death' and also that a 'persistent latent rickettsial infection is possible despite successful and adequate antibiotic treatment'. The subjects were to be recruited from subordinate staff of the responsible research unit and to sign a consent form". (2)

(Note well: this quotation is not from a pre-Nuremberg document; the document is post-Helsinki/Tokyo.)

c) In their recently-published international survey of oncologists' (n = 170) attitudes concerning the informed consent requirement vis-a-vis entry of their patients into randomized breast cancer treatment trials, Professors Taylor and Kelner of the University of Toronto provide this information in published form:

i) TABLE 7: Questions asked physicians relating to category 5: attitudes and patterns of behavior.

Question	Response	USA %	Can. %	Eng. %	Scot. %	Aus. %	Fra. %	Swed. %	Ita. %	Total %
(H) I obtain informed consent before placing eligible patients on randomized clinical trials	Always	79	83	84	80	100	33	29	0	69
	Sometimes	18	0	8	0	0	0	42	0	9
	Never	3	17	8	20	0	67	29	100	22

ii) TABLE 4: Questions asked physicians relating to category 2: doctor patient relationship

Question	Response	USA %	Can. %	Eng. %	Scot. %	Aus. %	Fra. %	Swed. %	Ita. %	Total %
(H) When my patients sign the informed consent sheet, they are aware that they are a research subject in an experiment	Always	15	12	33	20	29	7	29	7	15
	Sometimes	44	33	25	20	43	33	43	36	38
	Never	41	55	42	60	29	60	29	57	47

iii) **TABLE 5: Questions asked physicians relating to category 3: regulates formerly flexible decisions**

Question	Response	USA %	Can. %	Eng. %	Scot. %	Aus. %	Fra. %	Swed. %	Ita. %	Total %
(D) Informed consent regulates	Always	20	14	42	20	29	27	42	0	20
what I tell my patient on randomized	Sometimes	52	48	25	20	29	53	29	57	47
clinical trials	Never	28	38	33	60	43	20	29	43	33

The authors conclude: "It was clear that the physicians in all the eight countries involved (France, Italy, Sweden, U.S.A., Canada, Australia, Scotland and England) questioned the legitimacy of informed consent" (3). (Note well: the survey discussed here was done within the last six months).

The point has been made by Towers (4) and others, including the Chairman of one of yesterday's sessions, that education regarding research ethics should be part of the researcher's preparation, at least at the pre-professional stage. In our own organization (Westminster Institute for Ethics and Human Values - London, Ontario - Canada), for example, this imperative has been translated into initial action; we have now committed $250,000 over the next three years to enter on the work of research education of the pre-professional, the practitioner and those in the community. The purpose of this research is to stress the notion of integration of ethics with educational preparation.

In view of continuing developments in this area, continuing research ethics education of practicing researchers seems as necessary as their continuing education in the area of their research practice. In fact, however, formal research ethics education is not common in health science faculties in this country or elsewhere; this state of affairs can be observed by any who care to examine it. While there are programs in medical ethics taught at the non-professional university level, the amount of time devoted to formal investigation of research ethics in these programs within health science faculties, is very limited. Further, it appears that on-the-job research ethics teaching is not common, either. Consider the following information, e.g. from the report already cited:

TABLE 7: Questions asked physicians relating to category 5: attitudes and patterns of behavior

Question	Response	USA %	Can. %	Eng. %	Scot. %	Aus. %	Fra. %	Swed. %	Ita. %	Total %
(E) I was taught the technique of explaining informed consent to patients	Yes	13	19	33	20	29	13	14	36	19
	No	87	81	67	80	71	87	86	64	81
(F) I train my staff in the technique of obtaining informed consent	Yes	16	10	17	20	14	13	29	14	15
	No	84	90	83	80	86	87	71	86	85

The various transnational statements of standards, for "ethical research" make no reference to education regarding it. To sharpen the point, the WHO/CIOMS document has this comment: "29. An important secondary objective of externally sponsored research should be the training of health personnel of the host country to carry out similar research projects independently". Should there not be some parallel statement regarding the first focus for these documents, i.e., concern for ethics education?

Clearly, the purpose for work on these documents was more than the affirmation of the concepts: necessary, but not sufficient. If the documents are to have the desired impact, then education regarding their content seems imperative. Of course, it could be argued that the prospective research ethics review process provides some education in this area. Thus, researchers and committee members learn research ethics in practice, or on the job so to speak; by ripple effect, their peers learn as well. It could also be argued that those engaged in conferences like this, even as those who write and read in this area --whatever the level -- are being educated as they undertake such activity. The numbers of persons involved in such activity is relatively small, however. How then to reach the public? How to reach future researchers? How to inform research ethics committee members regarding developments not within their own experience? In fact, individual research ethics review committees do not have the formal education of their membership - initial, ongoing - or of those beyond that membership as part of their mandate, generally speaking. If it be argued that such education is more properly a national concern, it is not clear which national body within any country ought to be responsible for such education. Again, since these documents are transnational in character and future documents are to be transnational in character, should there not be some effort at transnational education carried out by a transnational body?

In the end, it may be that such education will not prevent abuse; the good that is known is not always performed. To quote an anecdotal comment taken from the report already cited is apt here:

> "There are many ways of skinning a cat...if you get my message... When a patient says to me, Dr., what should I do, and I say, I think you should sign here, that's all they need to know. So in fact, I got so-called, 'informed consent' because you have her signature on the paper, but give me a break...the patient is scared to death and is not in the least interested in the mass of information on the form. So yes, I guess I get informed consent from all my patients, but do I?" (3).

The response to this comment, and to the more general attitude it conveys, cannot be that education in this area be abandoned; needed instead is a strengthening of it, with an attempt to try to provide better motivation for doing what ought to be done.

A second recommendation, then, towards refinement and expansion of the standards:

(1) to identify the need for education in this area, i.e., research ethics education at both the professional and the public levels;

(2) to research and suggest methods for implementing such education.

Area # 3 - Epidemiology: The Need for Intensive and Innovative Attention

In elaborating our concern for protection of the individual subjects of research procedures, we have left many questions unaddressed. For example, we have not discussed the use of patients in certain non-clinical research ways: experimental projects in the areas of medical anthropology, medical psychology, medical sociology. We have not made mention either of the question of self-experimentation. These are very important areas in the context of research ethics; they, and several other unaddressed research ethics areas, should surely be addressed by those concerned with transnational standards for research ethics.

Of particular concern for today's meeting: research on groups. We have given no more than passing attention to the ethical questions arising in this area, yet it is one of obvious importance in any approach to formulation of transnational standards. Previously-drafted ethics documents have given it some attention, e.g. the CIOMS/WHO statement. The ethical issues arising in such research may be seen as an extension of issues we have already addressed: who is to consent for the group when the group as a whole is the research subject; what information should individual group members have; how prevent their coercion in terms of participation? Again, in showing respect for subjects, how adjust for cultural differences when the group's value system may differ from that of the researcher? Is privacy important to these particular people, for example? What about choice? As Dr. Levine pointed out in a notable statement at an earlier CIOMS conference (5), will our standards apply there? Should they? Will mere observation of these people, since they are 'different', be disrespectful of them? Will it reduce their cooperation if we seek to explain our observational methods? What interventions are appropriate when knowledge for this particular group's benefit is the goal? How are we to determine their benefit? Which interventions would carry risk to the group as a whole, even as there is concern for risk to the individuals who comprise the group? What is just with regard to work with such populations - just in terms of the individual and in terms of the group collectively? Our discussion touched on some of these concerns with regard to drug testing, e.g., with reference to drug testing programs, e.g., the infertility research programs mentioned by Dr. Barzelatto. In this connection, we heard something of the development of international standards for the conduct of such research. Have these standards a part in, are they to be the basis for, the approach of this Conference or its counterpart in refining and expanding transnational standards?

To move beyond the general question of group research now, and to speak precisely about epidemiological research, of an observational sort, very little has been said here. To members of this group, and with great respect to you, what is it appropriate for a lay person to say as regards the importance of epidemiological research in prevention of illness, promotion of health, collection of data, all of which are necessary for optimal planning/delivery of appropriate services?

Such epidemiological research will not require the ethical analysis appropriate to the concerns raised in highly invasive-interventional research. The ethical dilemmas posed by epidemiological research are no less real, however. As a specific example, and speaking in the main to clinicians, I would like to consider a fictitious AIDS study of the epidemiological variety. (I choose the example not only because the areas are important in their own right, but because the non-mention of AIDS and of epidemiological research represents a rather curious omission from this week's agenda).

In such a project, the investigator wants to know, _inter alia_:

(1) the time line - diagnosis of AIDS to patient's hospitalization;
(2) the time line - diagnosis of ARC among persons who are sexual contacts of those identified as having AIDS, from time of first sexual contact with AIDS victim once AIDS was diagnosed;
(3) the time line - diagnosis of AIDS after diagnosis of ARC among those persons who are sexual contacts of persons with AIDS as in (2) above;
(4) community resources now used by those with ARC/AIDS;
(5) add other desired variants.

Why is such knowledge useful, desireable? It will be used:

(1) to help design local community support services for this population in response to locally-specific needs - it may be used to enhance information and counselling service for this population, e.g.;
(2) to provide information regarding appropriate planning towards hospital service needs in this area;
(3) to provide base line and longitudinal information concerning onset and progress of ARC/AIDS - knowledge of fundamental importance towards cure of this malady.

What kinds of ethical questions must the research ethics committee consider here?

The fictitious Chairman's diary, with notes made prior to convening the committee meeting, reads: "What ought the committee's composition be? A very delicate matter. There is a certain competition evident among the researcher and those colleagues knowledgeable enough to comment on an AIDS project; it has to do with publication and with possible promotion in terms of early scientific reports on AIDS. How preserve the researcher's initiative and privacy here?" Again, "It is imperative that statistical validity be assured in this study. Does the proposal as presented demonstrate that capability? Who can tell us?"

As to specific ethical issues arising, the fictitious Chairman's (edited) notes read:

(1) Respect for person/privacy is the first priority.
With that in mind, how find appropriate research subjects for this project? If the patients' physicians ask for participation, will that be seen as coercive? What about inquiring among the blood-testing clinics or the blood transfusion services; again, there is the question of privacy. How balance privacy, coercion and the need for such research information?
What about sexual contacts? How enrol them as subjects, while preserving their privacy? Will they trust the researcher to keep information anonymous?
Will members of the research team be truly respectful of any subject's life style? How bring this point out to the researcher, tactfully and forceably?
There is concern for consent not only in terms of coercion, but in terms of age; some suggested subjects will certainly be under 18 (legal age for research consent in Ontario).
Should we put these young people in or out of the study?
When some of these subjects have been recruited, sooner or later, one of the research group must say, "You now have AIDS" How will the researcher do that; what about support for such patients, for their relatives and/or their significant others? How perserve the privacy of the diagnosis if the AIDS subject wishes this?
Looking to the subjects' consent, what is an appropirate form for consent here? Is the consent form submitted adequate in terms of listed benefits (any?) and harms (? psychological, physical, social) to these individuals?

(2) Harm to others is a concern.
The matter of blood-sampling to be done in observing these subjects raises a very delicate issue. In Ontario, AIDS is a 'reportable' disease, though not necessarily reportable with personal identity attached. The subjects at risk for ARC must be told that AIDS is 'reportable' so that they can

agree, knowledgeably, to participation in the study. The blood test which seems routine is thus more than routine; it involves a possible record for use of public health authorities.

Of course, some subjects who have been recruited will opt out on hearing this; what effect will that ha ve on the statistical data base required?

Some of the subjects at risk for ARC might say, "No problem about the blood test. I donated at the Red Cross a few years ago - they said nothing; I'm fine". They may say this before they are diagnosed as having ARC, but if their donation to the Red Cross was given before Red Cross donations were checked for sero-positivity, and if they are in fact sero-positive now, what does the ethics committee thus owe those who might have received such blood and who are now at risk because of the donor's possible sero-positive status at the time of the donation? What is the responsibility of the research ethics committee to any such blood recipient's sexual partner? Should privacy for the research subjects here outweigh concern for possible harm to others; should the committee keep secret the possibility that the blood received might have been contaminated?

What actual arrangements regarding confidentiality are in place for this study?

Is the ethics committee to be concerned with the research subject's non-reported contacts? Should such contacts be reached, however indirectly, as warning about safe sexual practices?

Of course, this is a research project; it is not an undertaking in preventive therapy - or is that distinction valid here?

(3) Harm/benefit for the subject is certainly a problem.

Should these subjects be warned (again) about continuing in their chosen lifestyles? They know and the committee knows they know that safe sexual practice should be observed. How 'paternalistic' is this committee to be? The other side of the question is equally difficult: will any warning given by the committee 'turn off' these subjects; the population is already quite fragile and statistical realiability is a concern.

(4) Scientific advance depends on publication; what problems will this raise?

The information must be disseminated while privacy is perserved. To respond to these two possibly conflicting norms, the local temper of the community must be judged. Of course, there will be concern for the agency (university?) reputation as scholarly, even as the agency (university?)

must be sensitive to the needs of the subject, researcher and community.
If the research subjects read newspaper reports about such research, how will it affect them? Is that a concern for the ethics committee?

(5) Possible harm to the research associates; consider this carefully.
These people are legitimately concerned for their own well-being: needlestick injuries, working in an environment in which contact with bodily fluids and the like is possible. Will they have adequate protection in the research environment? Is one of the concerns for the ethics committee a course of education for research personnel?

The fictitious Chairman's diary had many more pages; the ethical concerns raised seemed endless. The actual meeting of the research ethics committee brought out further ethical problems...

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Similar scenarios could be devised concerning other types of epidemiological study, for example, the study of records only with no use of presenting subjects. The ethics problems of this kind of research would not be easier (or more difficult) than those already described; epidemiological ethics is not simple. If, for example, a study concerning lung cancer among abstestos mine workers is proposed, and if records only are to be used, the familiar issues already raised will surface again. Thus: how have access to the records; how perserve privacy; what kind of consent is required? For those records in which it is indicated that the individuals are now dead, what kind of permission is needed? If relatives must be approached to give permission for access to the records, what kind of information ought they be given? All of this is easily said, but not so easily arranged.

Still in the line of possible epidemiological studies, suppose either of the two studies noted (or a variant of them) were re-located so that the culture of the researcher was not the culture of the research subjects. What ethical questions arise in pursuit of 'foreign' epidemiological studies, for example?

To conclude here, a third recommendation to this group:

> that the ethical aspects of epidemiological studies and the appropriate responses of the ethics committee to such studies be the subject of immediate and intensive research effort for any ongoing research ethics group this Conference proposes to sponsor.

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Overall, with reference to the three points made here: there seems to be a clear need to consider the international statements before us today, not only in theoretical terms but also in terms of their practical implications. Further, if the growing vision of research ethics is that of continuing concern for the research subject in an interdependent world, then the need for attention to all kinds of human subject research as well as to matters of justice, self-direction, benefit, and no harm is imperative. If justice and the various other concepts now affirmed in the documents are to be realized in practice, then some attention must be given to further education regarding them. The good example provided in the statements by way of declarations is laudable and necessary. However, if the statements are to have proper binding power in the moral order, they must be made known and some effort must be made to enhance compliance with them. Beyond education regarding the material in available research ethics documents, we must continue to press for ever more appropriate standards of research ethics and for an ever more intelligent approach to the functioning of those committees designated to work with such standards. All these will require ongoing effort in several dimensions. Groups like this one should be primary activators in such effort.

Footnotes

1. Z. Bankowski and J.F. Dunne, "History of the WHO/CIOMS Project for the Development of Guidelines for the Establishment of Ethical Review Procedures for Research Involving Human Subjects: in Human Experimentation and Medical Ethics (XV CIOMS Round Table Conference), ed. Z. Bankowski and N. Howard-Jones, Council for International Organizations of Medical Sciences (Geneva 1982) p. 447.

2. *Ibid*., p. 449.

3. K.M. Taylor and M. Kelner, "Informed Consent: The Physicians' Perspective" in Soc. Sci. Med. (v. 24, n. 2) pp. 135-143, 1987.

4. Cf. report of discussion in Medical Ethics and Medical Education (XIV CIOMS Round Table Conference), ed. Z. Bankowski and J. Corvera Bernardelli, Council for International Organizations of Medical Sciences, (Geneva 1981) p. 154.

5. R.J. Levine, "Validity of consent procedures in technologically developing countries" in Z. Bankowski and N. Howard-Jones, *op. cit.,* pp. 16-30.

DISCUSSION: Gustav-Adolf Martini

I would like to begin by expressing my considerable respect to Dr. Lynch. I am particularly grateful to her for having taken up the subject of epidemiology which was already briefly raised in the discussion of one of the former sessions. I think this is a critical prerequisite for essential and urgently needed measures in preventive medicine. With the example of AIDS she has illustrated the huge ethical problems involved that we encountered at a much lesser scale twenty years ago with the occurrence of the Marburg Virus disease. At that time the sexual transmission of a systemic viral disease was unknown and incidentally observed for the first time. The "new" way of transmission turned out to be particularly important in the spread of Virus Hepatitis B and late in the fateful spread of AIDS with all the ethical implications involved by the way of transmission in certain risk groups of the population.

Dr. Lynch's report based itself on the existing use of the current guidelines to highlight certain experiences. First of all it showed that guidelines such as the Helsinki resolutions are really not well known amongst the younger medical investigators. Secondly, it referred to the lack of sufficient information to many patients about the dangers and risks of treatments or experiments. Thirdly, it also complained about the unsatisfactory state of training in medical ethics worldwide and required that the subject of medical ethics be included in general medical education. Finally the report asked whether more fairness could be applied in distributing results of scientific research.

With regard to the subject of the report which was the possibilities for refinement and expansion of transnational standards, I would like to emphasize what was discussed at several occasions during the conference: the need for more in depth ethics study during the whole medical training period and at the postgraduate level.

It has sometimes been argued whether and how medical ethics should be taught and who is prepared to do it. The subject of medical ethics is a difficult one and needs special knowledge, attitudes and life experience. Life sciences, medicine, humanities and the social sciences should all be recognized as integral parts of medical education. The training should be problem - and person (case) - oriented and there should be regular discussions at staff rounds and conferences where the elder staff members participate.

I do not think, however, that we are sufficiently prepared and well-equipped with trained staff so far, at least not in the Federal Republic of Germany. As far as I know, in Western Europe there is only one chair for medical ethics, that is in Maastricht, Netherlands.

A few weeks ago, the medical faculties in Germany were called on by the responsible board of regional ministers of education (Laender Minister fur Wissenschaft und Kultur) to strengthen medical ethics in the training programme for medical students. It would be very useful if in this Conference we were able to arrive at a resolution for the setting up of chairs for medical ethics in medical schools and in some special institutions. Such institutions could act in a public fashion in order to improve the kind of information which is not always provided very clearly and correctly by the media. Such centres could also train persons to serve, for example as consultants to Ethics Committees.

In this connection I would also like to refer to the efforts made recently by the professional medical associations and researchers in the field of surgery and internal medicine. The book "Principles and Practices of Research Strategies for Surgical Investigators" by an international group of surgeons, Troidl, Spitzer, McPeek, Mulder and McKneale, as well as the "Handbook for the Academic Physician" by McGalski and Frey (both Springer Publ., Heidelberg and New York, 1986) contain detailed and excellent chapters on medical ethics.

This brings me to the second main issue: expansion of transnational standards. Leading researchers in surgery from the countries represented here at this conference have published reports on the situation in their respective countries. Together with the impressive report by Mr. Suzuki, that we heard here during the conference, the Japanese contribution in the mentioned surgical book entitled "Japan's Integration of Eastern Values and Modern Science" by surgeons Aoki and Muto is particularly interesting. The Japanese attitude vis à vis animal experiments is rather positive. At the same time the attitude vis à vis clinical trials is extremely negative. The reason for this is that the Japanese public believes that treatment should be carried out on a given patient only once animal trials have demonstrated that it is effective, and the treating physician himself has convinced himself that his offered treatment is the best available. Therefore it is apparently quite impossible or extremely difficult to obtain willing participation in clinical trials. Doctors who admit that they are unable to determine what is the best treatment for their patient lose the trust of the patient and even of their own professional peers.

Even in Europe we have difficulties when multicentre studies are carried out with groups from different nationalities. To give an example, a large scale inter-European study in Crohn's disease was interrupted by the Scandinavian partners when the trial organizers adopted a requirement for a written consent by the patient. The reason for this was that the relationship of trust would be burdened too much by written consent. In many countries, trust in the physician is the very basis for therapy. Otherwise, one cannot explain the vast difference observed in the placebo effect from one country to the other, e.g. in the treatment of peptic ulcer. Also the doctor as a placebo plays a different role from country to country.

We have repeatedly and explicitly stressed the autonomy of the patient at this conference. In some other cultures and civilizations, the family and the community in which he lives are considered to be just as important as the patient. Tristram Engelhardt reported that in China the village community and the family members are often paramount to one's own opinion in settling conflicts and also in obtaining consent. Sensitivity to other cultures should therefore be one of the major concerns of ethics, especially in the framework of international cooperation and multicentre trials.

Taking into account the pecularities and traditions of ethnic groups within our own pluralistic societies means that one has to be flexible, but does not mean that one should circumvent some of the basic principles on which we are trying to reach agreement.

To conclude: it would be worthwhile perhaps not just to ask for the informed consent of the patient but also, as has already happened once in the 1930's during the Weimar Republic in Germany, to ask for the informed consent by the researching physician who would agree explicitly to comply with the ethical principles, as our medical ancestors did through the Hippocratic Oath.

Document 15

APPENDIX: A BIBLIOGRAPHY ILLUSTRATING THE U.K. APPROACH TO BIOETHICS

ANNEXE: BIBLIOGRAPHIE ILLUSTRANT L'APPROCHE ADOPTEE AU ROYAUME-UNI EN MATIERE DE BIOETHIQUE

John Fairclough, Gordon Dunstan, Raymond Hoffenberg

International Summit Conference on Bioethics
Colloque international de bioéthique

CABINET OFFICE
70 Whitehall London SW1A 2AS Telephone 01-233

6 April 1987

Dear Fellow Delegates,

INTERNATIONAL SUMMIT CONFERENCE ON BIOETHICS - OTTAWA 1987

In preparing for the Ottawa Conference I and the other members of the UK team, felt it might assist delegations to appreciate better the UK perspective on many of the topics on our current agenda, if they could be given some background, in advance, on the UK approach to bioethical problems.

Therefore, we have put together the attached summary and bibliography, along with some key literature, which we believe illustrate well the way in which the UK addresses bioethical issues of various kinds. We also hope you will find the reading provides some interesting and stimulating ideas of wider relevance to the whole area we will be considering together during the course of the coming week.

The members of the UK team are looking forward to the conference and the opportunity it provides to discuss in more detail increasingly important questions relating to the ethics of research with human beings, which are of common international concern at the present time.

Yours sincerely,

John Fairclough

THE UK APPROACH TO BIOETHICAL PROBLEMS

1. The UK's approach to bioethical problems can be characterised as creating a very light framework of statute law, within which guidelines can be established, enforced, monitored and modified as necessary by informed bodies normally with substantial lay involvement. Such bodies range from the General Medical Council, which is statutorily responsible for the regulation of the medical profession, to local hospital ethical committees. The lay interest can also be brought to bear through the common law, which on occasion tests current practice against statute and also against general lay opinion. But in any event the concept of "case law" as a basis for establishing and modifying guidelines is central to the whole process.

2. This UK approach can be seen as intermediate between two extremes. One is to leave all such problems to individual practitioners, perhaps guided by their professional bodies. The disadvantage of this approach is the decoupling from society at large; ethics established in this way can easily diverge from what the general public is prepared to accept as reasonable, or can be portrayed as likely to do so. The other extreme is for ethical codes to be established by statute, whether national or international. The disadvantage of this approach is rigidity, since it is difficult for codes established in this way to respond to changing circumstances and hard cases. Both extremes share the disadvantage that they discourage continuing wide debate on ethical problems. There is a risk, not always entirely avoided in the UK, that the purely informal approach will, in some particular area, allow what is seen as a public scandal which may then be followed by the opposite extreme of hasty and over-detailed legislation.

3. The UK approach described is just that: a way in which problems tend to be approached, rather than a formally worked out and stated policy. It is also an approach which stresses pluralism and wide debate. It is therefore unsurprising that the means and the institutions through which it is operated are therefore varied and have changed over time. A particular feature, however, is that learned bodies (the Royal Colleges of Medicine) have played a stronger part that their counterparts in many other countries. Rather than attempt further abstract analysis, it may be more helpful to illustrate how this process has worked through some examples. The examples have been deliberately chosen to range more widely than research on human subjects, because the UK approach is wider in its application, and provides the context within which the UK tends to address specific issues.

EXPERIMENTS WITH ANIMALS

4. Legislation to protect experimental animals has existed in the UK since 1876. The Cruelty to Animals Act of that year established the crime of causing needless suffering to animals and provided penalties. Within the framework of this law the Home Office set up an Inspectorate, staffed by physicians and veterinary surgeons, and an Advisory Committee which advised the Home Secretary on general policy and on the merits of particular protocols for research. Since the mid-1970's the Advisory Committee has included lay members as well as an independent chairman. Successful as the control of animal experiments was under the 1876 Act - and without resort to criminal prosecution - it was considered obsolete because of the increased range of experiments and number of animals involved - much of it required by safety legislation - and of new techniques in research, some of which were more invasive, while some reduced the need for live animals as experiment subjects. More understanding of animal physiology, especially in neurology, extended the range of protection due. The recent Statute, therefore, the Animals (Scientific Procedures) Act 1986, was prepared out of long experience in the laboratories, the Inspectorate, the Home Office and the process of consultation and advice both through an advisory committee and more generally through the issue of two White Papers.

5. The new Statute incorporates that experience. Its purpose is to permit the conduct of essential research on animals - that is, research for which no alternative method can be used - provided that the method is adequate to yield valid results, and that the suffering (if any) inflicted on the animal is not disproportionate to the beneficial knowledge sought. An inviolable termination condition requires the immediate despatch of any animal found to be in unwarrantable pain or distress. The Advisory Committee is given statutory place and powers as the Animal Procedures Committee, and places are found on it for members of those responsible voluntary organizations concerned for animal welfare which contributed constructively to the long Parliamentary process toward enactment. Pressure for the replacement of animals in research, by means of computer models, tissue cultures and the like, is maintained by voluntary bodies with support from Government funds. Guidelines for the implementing of the Act, though issued with the authority of the Home Office, have been drawn up with the assistance of the Royal Society - the supreme independent academy of the scientists - and the Universities Federation of Animal Welfare, another voluntary body. The intention of the legislature, and of the Home Office, within the framework of the new Statute, is to build on the foundation which srved well in the control of animal experiments over the last century: that is, on trust between the

laboratories, the Inspectors, the civil servants administering the Department, and the new advisory body, all of them answerable, ultimately, to the Crown in Parliament.

BRAIN DEATH

6. With the increasing use of intensive care techniques for deeply comatose and unresponsive patients with severe brain damage, it was recognised in the early 1970's that criteria were needed which would indicate permanent functional death of the brain and therefore allow mechanical ventilators to be switched off in the secure knowledge that recovery of the patient would not take place. At the request of the Department of Health and Social Security a Working Party was established by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom to consider these criteria. In October 1976 a statement was issued by the Conference which laid down conditions for considering the diagnosis of brain death and tests for its confirmation.

7. At various times in the past 10 years public or professional concern about the validity of the criteria has caused the Conference to re-examine them. In 1979, the Conference published a memorandum "Diagnosis of death" in which it noted that "brain death represents the stage at which a patient becomes truly dead". The Conference's statements of 1976 and 1979 were distributed by the Department of Health and Social Security (DHSS) to all hospital doctors in 1980.

8. In 1983 the DHSS circulated a booklet entitled "Cadaveric Organs for Transplantation" to all hospital doctors. This was a report of a separate Working Party set by the UK Health Departments, representing in slightly modified form the views expressed by the Conference. It is important to note that this document was subtitled "Code of Practice" and was intended as a "set of basic guidelines which could be amplified to suit local circumstances".

9. Towards the end off 1986, a heart transplant operation was performed in England on an infant using an organ taken from a newborn anencephalic. This raised new ethical considerations. The DHSS asked the Conference of Colleges to set up a further Working Party to advise about transplantation in infants in general and the use of organs from an anencephalic in particular. This Working Party advised the DHSS to establish a moratorium on all transplantation in infants until its report had been finalised. In a circular letter in February 1987, the Chief Medical Officer of DHSS wrote to all Regional Medical Officers recommending a moratorium and saying "I hope it will be heeded by all transplant surgeons".

10. This resume illustrates the advisory and facilitatory role taken by the DHSS and its reluctance to issue absolute directives on ethical issues. It also illustrates the important function of the Conference of Royal Colleges in providing professional advice to the DHSS on such issues.

IN VITRO FERTILISATION (IVF) AND EMBRYO RESEARCH

11. The first child resulting from IVF was born in the UK in 1978. Whilst giving considerable new hope to infertile couples the occasion also posed a number of ethical problems for the medical profession. In response to the profession's need for guidance with regard to research in the field of IVF the Medical Research Council (MRC) immediately set up an advisory group which published its guidelines in the British Medical Journal in 1982. The following year the Ethics Committee of the Royal College of Obstetricians and Gynaecologists (RCOG) published its own report and guidance. In 1982 also the Government set up a Committee of Inquiry into Human Fertilisation and Embryology under the chairmanship of Dame Mary (now Baroness) Warnock. The report of the Warnock Committee was published in 1984: one of its principal recommendations was that a statutory authority should be established to regulate both research and certain types of fertility service. Some members at least were conscious of the example of the model offered by the regulation of animal experiments. Both during and after the work of the Warnock Committee, there was a considerable public debate; contributions from outside Government included publications by the Council for Science and Society, the Church of England Board for Social Responsibility, and the Ciba Foundation.

12. In the public and Parliamentary debate that followed the Warnock report, it became obvious that there was not yet a sufficient consensus, particularly on research with human embryos, for legislation to be passed. As an interim measure the MRC and the RCOG agreed jointly to set up a Voluntary Licensing Authority (VLA). This Authority was established in March 1985 under the chairmanship of Dame Mary Donaldson. It now regulates IVF and embryo research in the UK, and is the only such regulatory body in the world. As its title indicates the VLA is voluntary and has no statutory powers, but it has in fact established quite substantial authority in its area. In December 1986 the Government published a consultation paper formally requesting views on human infertility services and embryo research from interested bodies and individuals including the MRC and the VLA. It is expected that legislation will be introduced

in the next Parliament.

13. A further illustration of the UK approach is provided by some of the publications which this process has generated, many of which have made valuable contributions to thinking on particular issues. Attached is a list of publications which may be of particular interest to you.

A BIBLIOGRAPHY ILLUSTRATING THE UK APPROACH TO BIOETHICS

EXPERIMENTS ON ANIMALS

Scientific Procedures on Living Animals
Home Office, Cmnd 8883, HMSO, 1983

Guidelines on the Use of Living Animals in Scientific Investigations
The Biological Council, 1984

Scientific Procedures on Living Animals
Home Office, Cmnd 9521, HMSO, 1985

Animals (Scientific Procedures) Act 1986
HMSO, 1986

Guidance on the Operation of the Animals (Scientific Procedures) Act
Home Office, 1986

IN VITRO FERTILISATION AND EMBRYOLOGY

Human Procreation: Ethical Aspects of the New Techniques
Council for Science and Society, Oxford University Press, 1984

Report of the Committee of Inquiry into Human Fertilisation and Embryology
Department of Health and Social Security, Cmnd 9314, HMSO, 1984

Personal Origins: The Report of a Working Party on Human Fertilisation and Embryology,
Church of England Board for Social Responsibility, CIO Publishing, 1985

Research Related to Human Fertilisation and Embryology
Medical Research Council, 1985

First Report of the Voluntary Licensing Authority for Human *in vitro* Fertilisation and Embryology
Voluntary Licensing Authority, 1986

Human Embryo Research: Yes or No?
The Ciba Foundation, Tavistock Publications, 1986

Legislation on Human Infertility Services and Embryo Research: A Consultation Paper
Department of Health and Social Security, Cm 46, HMSO, 1986

BRAIN DEATH

Diagnosis of Brain Death
Statements by the Conference of Medical Royal Colleges and their Faculties 1976, 1979 and 1986

Cadaveric Organs for Transplant: A code of practice including the diagnosis of brain death
Health Departments of Great Britain and Northern Ireland, HMSO, 1983

RESEARCH ON HUMAN SUBJECTS

Responsibility in Investigations on Human Subjects
Medical Research Council, 1962

The Use of Foetuses and Foetal Material for Research
HMSO, 1972

Clinical Trials - Compensation for Medicine-induced Injury
Association of the British Pharmaceutical Industry, 1983

Code of practice for the Clinical Assessment of licensed Medical Products in General Practice
Association of the British Pharmaceutical Industry, 1983

Responsibility in the use of Personal Medical Information for Research: Principles and Guide to Practice
Medical Research Council, 1985

Medical Research with Children: Ethics, Law and Practice
Institute of Medical Ethics, Oxford University Press, 1986

Research on Healthy Volunteers
Royal College of Physicians, 1986

PRINCIPLES AND PRACTICE OF MEDICAL ETHICS

Guidelines on the Practice of Ethics Committees in Medical Research
Royal College of Physicians, 1984

Philosophical Medical Ethics
Raanan Gillon, John Wiley and Sons Ltd, 1985

Handbook of Medical Ethics
British Medical Association, 1986

Research Ethics Committees
Supplement No. 2 to the IME Bulletin
Institute of Medical Ethics, September 1986

Informed Consent
Supplement No. 3 to the IME Bulletin
Institute of Medical Ethics, December 1986

Evolution and Mutation in Medical Ethics
G.R. Dunstan, reprinted from Ethical Dilemmas in Health Promotion,
John Wiley and Sons Ltd, 1987

MISCELLANEOUS

The Relationship between Physicians and the Pharmaceutical Industry
Royal College of Physicians, 1986

Journal of Medical Ethics, Volume 12 Number 4, December 1986
Institute of Medical Ethics

Bulletin No. 18, September 1986
Institute of Medical Ethics
Bulletin No. 19, October 1986
Institute of Medical Ethics

Bulletin No. 21, December 1986
Institute of Medical Ethics

Bulletin No. 22, January 1987
Institute of Medical Ethics

RESUMES OF THE DELEGATES
NOTICES BIBLIOGRAPHIQUES DES DELEGUES

International Summit Conference on Bioethics
Colloque international de bioéthique

Ottawa, Canada, 1987

Prof. Koichi Bai was Professor of Law at Tokyo Metropolitan University and Professor as well as Director of the Institute for Medical Humanities at Kitasato University from April 1987. His specialties are civil and medical law. His publications have dealt with topics such as medico-legal approaches to the concept of death, medicine, law and ethics, and medicine and human rights.

Dr. Zbigniew Bankowski has been Executive Secretary of the Council of International Organizations of Medical Sciences since 1975. Here he directed the preparation of International Guidelines for Research Involving Human Subjects and Animals. His research background is in pathology and histochemistry.

Dr. Jose Barzelatto is Director of the Special Program of Research Development and Research Training in Human Reproduction of the WHO. A physician and endocrinologist, he has specialized in the management of international research programs, both for WHO and for the Organization of American States.

Dr. André Boué is a Professor in the Faculty of Medicine of the University of Paris. His fields of interest center upon fertility, fetal pathology and research involving the fetus and the embryo.

Dr. Henri Bricaire is a member of both the Royal Academy of Medicine of Belgium and of the National Academy of Medicine of France. His medical career has followed essentially a clinical direction. His fields of interest have been pathology and endocrinology.

Prof. Gordon Dunstan is Chaplain to Her Majesty, the Queen of England. He is also Professor Emeritus of Moral and Social Theology at King's College, University of London and Honorary Research Fellow, University of Exeter. He chaired the working party on reproductive technologies of the Council for Science and Society and serves on the Voluntary Licensing Authority to implement recommendations of the Warnock Commission. He has written on such topics as ethics, duty and consent in medicine.

Prof. Dr. Albin Eser is Director of the Max-Planck Institute for Foreign and International Criminal Law in Freiburg/Breisgau. His publications deal mainly with criminal law and its relation to ethics, focusing on topics such as suicide and euthanasia, sterilization and abortion.

Mr. John Fairclough is the British government's Chief Scientific Advisor. He is the Director of Manufacturing and Development for IBM UK and Chairman of IBM UK Laboratories. He is on secondment from IBM UK to develop science strategies for the British government.

Dr. Liborio Falanga is a lawyer by training. He is currently with the Office of Study and Legislation of the Ministry of Health. His work includes consideration of issues relating to organ transplants, as well as dealing with criteria for the definition of death.

Prof. Paolo Maria Fasella is Director General for Research, Science and Development and is head of the Joint Research Centre of the EEC in Brussels. He is the European Community's representative in the Eureka Group. Prof. Fasella has worked extensively in the field of biotechnology and is especially interested in viral proteins and clinical tests.

Dr. Henry Friesen is Professor and Chairman of Physiology and Professor of Medicine at the University of Manitoba. He has contributed extensively to the field of endocrinology. He is on the Executive of the MRC and a member of the Standing Committee on Ethics in Experimentation of the Medical Research Council.

Prof. Evangelos Garelis is a physician specializing in neurology and psychiatry and is currently the Vice-President of the National Drug Organization of Greece. He is also the Director of the Department of Psychiatry at Athens General Hospital where he holds both clinical and teaching positions.

Dr. Shigeaki Hinohara is President of St. Luke's College of Nursing in Tokyo as well as being a Consultant in Graduate Medical Education of St. Luke's International Hospital, and Chairman of the Life Planning Center, Tokyo. Dr. Hinohara is a member of the Ad Hoc Committee on Life Sciences and Mankind of the Council for Science and Technology, Science and Technology Agency.

Sir Raymond Hoffenberg is the President of the Royal College of Physicians of London, a Professor of Medicine at the University of Birmingham, a Senior Scientist of the MRC Clinical Research Centre, as well as a member of the Medical Research Council (U.K.). His research field is endocrinology.

Prof. Per Juul is the Chairman of the Drug Registraton board of the Danish National Board of Health, as well as being a member of that Board's Adverse Drug Reactions Committee. He is the Chairman of the Danish Society for Toxicology and Pharmacology and a member of the Toxicology Steering Committee of the European Science Foundation.

Dr. Abbyann Lynch, a philosopher, is the Director of the Westminster Institute for Ethics and Human Values. She chairs the University of Toronto's Policy Committee on the use of Human Research subjects. She has, amongst other committees and task forces, served on the Canadian Institute for Advanced Research Moral Values Task Force.

The Hon. Mr. Justice T. David Marshall is a Supreme Court Justice of the Northwest Territories and Justice of Appeal of the Northwest Territories and the Yukon. Dr. Marshall, also a physician, is Chairman of the Medical Research Council's Standing Committee on Ethics in Experimentation. The Committee is responsible for preparing new guidelines for the ethics of research with human subjects.

Prof. Dr. Gustav-Adolf Martini is Professor Emeritus at the University of Marburg, where he was Director of Marburg University Clinic. Prof. Martini is a member of several international medical associations, as well as co-editor of several leading medical journals.

Dr. Charles McCarthy is the Director of the Office for Protection from Research Risks of the National Institutes of Health. Previously he was Staff Director of the Ethics Advisory Board for Health, Education and Welfare. He is also the Chairman of the Interagency Co-ordinating Committee for the Protection of Human Research Subjects.

Mr. Jean Michaud is a member of France's National Consultative Committee on Ethics and Counsellor to the Supreme Court of Appeal. His interest in public and civil law is evident in the positions he has held; Examining Magistrate, Deputy Inspector-General of Legal Services, and Vice-President of the Court of Conflicts.

Dr. Russel Patterson is Professor of Neurosurgery at Cornell University Medical College. He is Vice-Chairman of the American Medical Association's Council on Ethical and Judicial Affairs. He has published extensively in the area of neurosurgery.

Prof. Dr. Gunther Patzig has studied classic philology and philosophy. He is a Professor at the University of Goettingen and Director of the Philosophic Institute. He is a member of the Goettingen Academy of Sciences and has published works on Aristotle, logic, ethics and metaphysics.

Dr. Edmund Pellegrino is Professor of Medicine and Medical Humanities at Georgetown University and Director of the Kennedy Institute of Ethics. Besides his scientific articles, he has written many general articles on medicine, medical education and philosophy.

Prof. Vittorio Sgaramella is Professor of Molecular Biology in the Department of Genetics and Microbiology of the University of Pavia. He is interested in genetic engineering and biotechnology and has worked extensively in the area of risk assessment.

Monsignor Elio Sgreccia is the Director of the Centre for Bioethics at the Faculty of Medicine at the Universita Cattolica del Sacro Cuore. He is a member of the Commission of the Ministry of Health on Genetic Manipulation. His basic interests are in the principles of bioethics, including their application in transplantation and euthanasia.

Mr. Eiji Suzuki is President of Mitsubishi Chemical Industries Ltd. He is a member of the General Committee of the Economic Council of the Economic Planning Agency. He is also Chairman of the Research Association for Biotechnology, Chairman of the Life Science Committee of the Federation of Employers' Association and President of the Bioindustry Association. He is a member of the Bioethics Committee of the Japan Federation of Medical Doctors.

Le professeur Koichi Bai enseignait le droit à l'Université métropolitaine de Tokyo. Il enseignera et dirigera l'Institut Kitasato des sciences humaines et médicales, dès avril 1987. Spécialiste du droit civil et médical, ses écrits abordent des sujets médico-légaux tels que le concept de la mort, de la médecine, de la loi et de l'éthique et celui de la médecine et des droits de la personne.

Le docteur Zbigniew Bankowski est le secrétaire exécutif du Conseil des organisations internationales des sciences médicales depuis 1975 où il a dirigé l'élaboration des principes directeurs internationaux pour la recherche biomédicale impliquant des animaux. Son expertise englobe la pathologie et l'histochimie.

Le docteur José Barzelatto dirige le programme spécial pour la recherche et développement et la formation en recherche sur la reproduction humaine de l'OMS. Médecin et endocrinologiste, il est spécialiste en gestion des programmes de recherche internationaux, aussi bien pour l'OMS que pour l'Organisation des Etats américains.

Le docteur André Boué est professeur à la faculté de médecine de l'Université de Paris. Ses champs d'intérêt englobent la fertilité, la pathologie foetale et la recherche impliquant les foetus et les embryons.

Le docteur Henri Bricaire est membre à la fois de l'Académie royale de médecine de Belgique et de l'Académie nationale de médecine de France. Sa carrière médicale est essentiellement à vocation clinique. Ses travaux ont été consacrés à la pathologie et à l'endocrinologie.

Le professeur Gordon Dunstan, aumônier de Sa Majesté la Reine d'Angleterre, est aussi professeur émérite de théologie morale et sociale au King's College de l'Université de Londres et chercheur honorifique attaché à l'Université d'Exeter. Il a présidé le groupe de travail du Council for Science and Society sur les technologies de reproduction, et fait partie de la Voluntary Licensing Authority, qui veille à l'application des recommandations de la Commission Warnock. Ses ouvrages traitent de l'éthique, du devoir et du consentement en médecine.

Le professeur Albin Eser, docteur, est depuis 1982 directeur de l'Institut Max-Planck de droit criminel international et étranger à Fribourg-en-Brisgau. Ses publications relèvent principalement du droit criminel et de ses rapports avec l'éthique, et il a concentré son travail sur des sujets tels que le suicide, l'euthanasie, la stérilisation et l'avortement.

Monsieur John Fairclough est le Conseiller scientifique principal du gouvernement britannique. Il est directeur de la fabrication et du développement pour IBM Royaume-Uni et président des laboratoires IBM Royaume-Uni. Il a été détaché auprès du gouvernement britannique par IBM Royaume-Uni pour élaborer les stratégies scientifiques.

Le docteur Liborio Falanga est un avocat de formation. Actuellement au bureau des études législatives du Ministère de la santé, ses travaux traitent de questions relevant des transplantations d'organes, et aussi des critères de définition de la mort.

Le professeur Paolo Maria Fasella est directeur général pour les sciences, la recherche et le développement et chef du Centre conjoint de recherche de la CEE à Bruxelles. Il est le représentant de la communauté européenne auprès du Groupe Eurêka. Les travaux extensifs du professeur Fasella relèvent de la biotechnologie et il s'intéresse principalement aux protéines virales et aux essais cliniques.

Le docteur Henry Friesen, professeur de médecine et de physiologie, est directeur du département de physiologie de l'Université du Manitoba. Par ses apports marquants, il a largement contribué au domaine de l'endocrinologie. Il siège au Comité de direction du CRM et au Comité permanent sur l'éthique en expérimentation du Conseil de recherches médicales.

Le docteur Evangelos Garelis, médecin, neurologue et psychiatre, est actuellement vice-président de l'Organisation pharmaceutique nationale de la Grèce. Il est également directeur du département de psychiatrie de l'hôpital général d'Athènes où il enseigne et occupe également des fonctions cliniques.

Le docteur Shigeaki Hinohara est président du Collège de sciences infirmières St. Luke de Tokyo de même que conseiller pour l'enseignement de la médecine aux cycles supérieurs de l'hôpital international de St. Luke et Président du Centre de Planification de la vie, Tokyo. Le docteur Hinohara est membre du Comité spécial sur les sciences de la vie et l'humanité mis sur pied par le Conseil pour la science et la technologie, organisme de l'Agence de la science et de la technologie.

Sir Raymond Hoffenberg est président du Collège royal des médecins de Londres, professeur de médecine à l'Université de Birmingham et chercheur principal du Centre de recherche clinique du CRM. Il fait également partie du Conseil de recherches médicales (Royaume-Uni). Il s'intéresse à l'endocrinologie.

Le professeur Per Juul préside le Conseil d'immatriculation des produits pharmaceutiques du Conseil national danois de la santé et il siège également au Comité de ce Conseil sur les réactions adverses aux produits pharmaceutiques. Il est président de la Société danoise de toxicologie et de pharmacologie et membre du comité directeur de toxicologie de la Fondation européenne de la science.

Le professeur Abbyann Lynch, philosophe, dirige l'Institut Westminster pour l'éthique et les valeurs humaines. Elle préside le Comité de politique de l'Université de Toronto sur l'utilisation des sujets humains pour la recherche. Parmi les comités et les groupes de travail auxquels elle a participé, on compte le groupe de travail sur les valeurs morales de l'Institut canadien des recherches avancées.

L'Honorable T. David Marshall est juge à la Cour suprême des Territoires du Nord-Ouest et à la Cour d'appel des Territoires du Nord-Ouest et du Yukon. Egalement médecin, le docteur Marshall préside le comité permanent du Conseil de recherches médicales (CRM) sur l'éthique en expérimentation. Ce comité élabore de nouvelles lignes directrices en matière de recherche sur des sujets humains.

Monsieur Charles McCarthy est directeur de l'Office pour la protection contre les risques de la recherche des Instituts nationaux de la santé. Auparavant, il était directeur du Conseil consultatif d'éthique pour la santé, l'éducation et le bien-être. Il est également président du Comité de coordination des organismes pour la protection des sujets humains de recherche.

Le professeur Gustav-Adolf Martini, docteur, est professeur émérite à l'Université de Marburg où il dirigeait également la clinique de l'Université de Marburg. Le professeur Martini appartient à diverses associations médicales internationales et co-rédige plusieurs journaux médicaux de premier plan.

Monsieur Jean Michaud est membre du Comité consultatif national d'éthique de la France et Conseiller à la Cour de cassation. Il s'intéresse au droit public et au droit privé comme en témoignent les postes de magistrature qu'il a détenus en tant que juge d'instruction, inspecteur général adjoint des services judiciaires et vice-président du Tribunal des conflits.

Le docteur Russel Patterson est professeur de neurochirurgie au College de médecine de l'Université Cornell. Il est vice-président du Conseil des affaires juridiques et éthiques de l'Association médicale américaine. Il a beaucoup écrit dans le domaine de la neurochirurgie.

Le professeur Gunther Patzig, docteur, a étudié la philologie classique et la philosophie. Il est professeur à l'Université de Goettingen et directeur de l'Institut de philosophie. Membre de l'Académie des sciences de Goettingen, il a publié des écrits sur Aristote, et ses travaux portent sur la logique, l'éthique et la métaphysique.

Le docteur Edmund Pellegrino est professeur de médecine et de sciences humaines médicales à l'Université de Georgetown et directeur de l'Institut Kennedy d'éthique. En plus d'articles scientifiques, il a écrit sur la médecine, l'enseignement de la médecine et la philosophie.

Le professeur Vittorio Sgaramella enseigne la biologie moléculaire au département de génétique et de microbiologie de l'Université de Pavie. Attiré par le génie génétique et la biotechnologie, ses travaux extensifs portent sur l'évaluation des risques.

Monseigneur Elio Sgreccia dirige le Centre de bioéthique de la faculté de médecine de l'Universié catholique du Sacré-Coeur. Il est membre de la Commission sur la manipulation génétique du Minsitère de la santé. Il s'intéresse surtout aux principes de bioéthique, y compris leur application aux transplantations et à l'euthanasie.

Monsieur Eiji Suzuki est président des industries chimiques Mitsubishi Ltée. Il siège au Comité général du Conseil économique de l'Agence de planification économique. Il préside l'Association de recherche en biotechnologie, le Comité de sciences de la vie de la Fédération des Associations d'employeurs, ainsi que l'Association des bioindustries. Il siège également au Comité de bioéthique de la Fédération des médecins du Japon.